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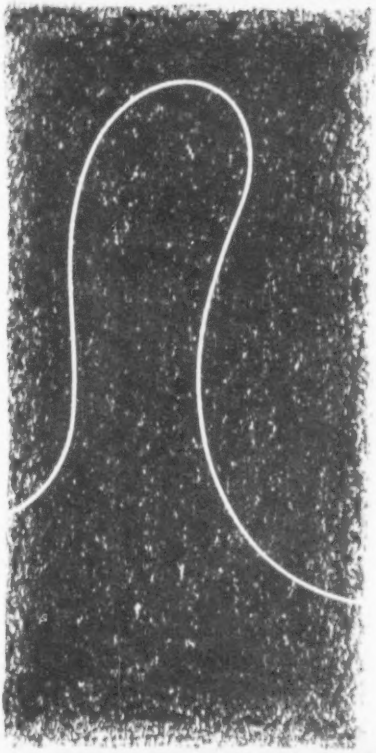

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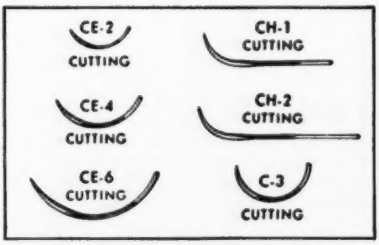

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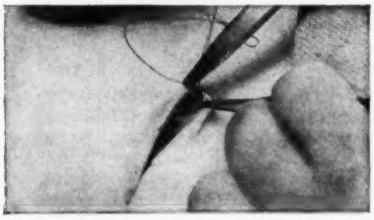

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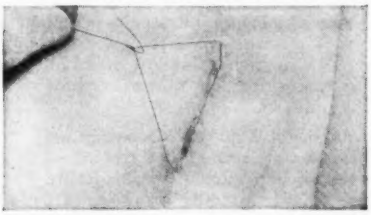

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RECURRING PANCREATITIS AND ASSOCIATED STENOSIS OF THE COMMON BILE DUCT

Treatment by Roux-Y Choledochojejunostomy

FRANK F. ALLBRITTEN Jr., M.D.
PHILADELPHIA

THE DIAGNOSIS of various phases of pancreatitis and their proper management have been long-recognized problems.[1] Little has been added to the description of the clinical features of the acute disease since that of Fitz in 1889.[2] These features are sufficiently characteristic in the acute and severe episodes of pancreatitis to generally permit reliable diagnosis. The less severe forms of the disease were, and are, frequently not recognized. Only since confirmatory laboratory tests have been readily available [3] has the frequency of pancreatitis become generally recognized. The severe forms of the disease as originally described by Fitz, and generally considered typical, are the fulminating episodes of pancreatitis. Less severe inflammatory reaction within the pancreas produces upper abdominal pain, various gastrointestinal symptoms, and no reliably detectable changes in the blood constituents or gastrointestinal secretions. The anatomical location of the gland, laboratory tests of function that indicate only extensive changes, and the lack of a means of roentgenologic demonstration of early changes in the organ result in failure to arrive at a specific diagnosis of early inflammation in most instances.

The histologic characteristics of inflammation of the pancreas are similar, though the disease may be secondary to trauma, a penetrating duodenal ulcer, or blood-borne or lymph-borne infectious agents, or of the commoner variety that seems to bear no relation to trauma or infectious agents. The latter may show the widest range of gross and histologic change, varying from slight edema to complete necrosis followed by fibrosis and, on occasion, calcification. Extensive fibrotic changes may cause an extraluminal obstruction of the intrapancreatic portion of the common bile duct. It is this feature that is of primary concern in the cases reported. It is evident that any treatment should take into consideration (1) the termination of the progress

From Jefferson Medical College and the Pennsylvania Hospital.

Read before the Section on Surgery, General and Abdominal, at the 102d Annual Session of the American Medical Association, New York, June 2, 1953.

1. Cattell, R. B., and Warren, K. W.: The Choice of the Therapeutic Measures in the Management of Chronic Relapsing Pancreatitis and Pancreatolithiasis, Gastroenterology **20**:1-14 (Jan.) 1952.

2. Fitz, R. H.; Acute Pancreatitis: A Consideration of Pancreatic Hemorrhage, Hemorrhagic, Suppurative, and Gangrenous Pancreatitis, and of Disseminated Fat Necrosis, Med. Rec. **35**:197-204, 1889.

3. Somogyi, M.: Diastatic Activity of Human Blood, Arch. Int. Med. **67**:665-679 (March) 1941.

of the disease and (2) the relief of symptoms. Common bile duct obstruction is followed by the usual symptoms of obstructive jaundice, and these may even predominate in the presenting symptoms of the patient.

Although the pancreas is an organ with a great functional reserve, recurrent destructive inflammatory episodes may result in demonstrable evidences of functional failure. Quantitative or qualitative decrease of the external secretions of the gland is indicated by disturbances of the function of the gastrointestinal tract, while the loss of the internal secretion from the gland is manifested by defects in the carbohydrate metabolism of the patient. Large portions of the gland can be removed surgically without demonstrable dysfunction of either internal or external secretion. Evidence of functional impairment following pancreatitis would suggest that extensive destruction of the gland had occurred.

Since the early work of Opie,[4] abundant evidence has accumulated to indicate that an ampulla common to the pancreatic duct and the terminal portion of the common duct may be of significance in the origin of pancreatitis. This evidence further indicated that regurgitation of bile into the pancreatic duct initiated and sustained the progress of the disease. Many have concurred in this opinion.[5] Numerous and extensive anatomical investigations have been conducted to try to determine the mechanism of regurgitation, and there has been considerable difference of opinion whether this theory of pathogenesis is tenable.[6] The rather common demonstration of the regurgitation of roentgenologically opaque material into the pancreatic duct during cholangiography with low intraductile pressure emphasizes the likelihood of this occurrence. Numerous investigators have confirmed the fact that the injection of bile into the pancreatic duct produces the typical gross and histologic findings of pancreatitis in the experimental animal.[5] This observation led Archibald to suggest that the occluding function of the sphincter of Oddi at the ampulla of Vater gave sufficient obstruction to permit regurgitation of bile into the communicating pancreatic duct. He suggested that division of the sphincter of Oddi was a logical procedure to prevent recurrent attacks of the disease.[5b] The recent demonstration by Doubilet and Mulholland of the mechanism of action of the sphincter of Oddi and the excellent results obtained after its division in patients with recurrent pancreatitis [7] have led to the adoption of sphincterotomy as a standard treatment for acute recurrent attacks of pancreatitis. Other suggested surgical procedures that have been most successful are those that have either reduced or eliminated biliary tract pressure by venting the bile before it reaches the ampulla of Vater, or those that have destroyed the communication between biliary and pancreatic

4. Opie, E. L.: The Etiology of Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp. **12**:182-188, 1901.

5. (*a*) Flexner, S.: The Constituent of the Bile Causing Pancreatitis and the Effect of Colloids upon Its Action, J. Exper. Med. **8**:167, 1906. (*b*) Archibald, E.: The Experimental Production of Pancreatitis in Animals as a Result of Resistance of the Common Duct Sphincter, Surg., Gynec. & Obst. **28**:529-545 (June) 1919.

6. Reinhoff, W. F., and Pickrell, K. L.: Pancreatitis: An Anatomic Study of the Pancreatic and Extrahepatic Biliary Systems, Arch. Surg. **51**:205-219 (Nov.-Dec.) 1945. Mann, F. C., and Giordano, A. S.: The Bile Factor in Pancreatitis, ibid. **6**:1-30 (Jan.) 1923.

7. Doubilet, H., and Mulholland, J. H.: Recurrent Acute Pancreatitis: Observations on Etiology and Surgical Treatment, Ann. Surg. **128**:609-638 (Oct.) 1948.

ducts. One of the former suggested by Bowers [8] seems particularly desirable, for the vent is established into a defunctionalized portion of jejunum rather than externally. This procedure would be particularly applicable in those patients with extraluminal stenosis of the common duct secondary to pancreatitis. Sphincterotomy would not serve to relieve the obstruction to the biliary tree in these peculiar circumstances.

The results of sphincterotomy, as advocated by Doubilet and Mulholland, have been found to be excellent, though there have been occasional failures.[9] From such failures one would suspect that factors other than obstruction by the sphincter alone were of some significance. In the cases to be reported, obstruction of the common duct above the sphincter of Oddi by stenosing pancreatitis had produced obstructive jaundice. Less severe obstruction in the pancreatic portion of the common bile duct may be responsible for persistence of symptoms after the division of the sphincter of Oddi, and this possibility should be taken into consideration when determining the procedure to be utilized at the operating table.

REPORT OF CASES

CASE 1 (Pennsylvania Hospital Record No. 87083).—A 57-year-old Negro man was admitted to the hospital Aug. 25, 1949, with the chief complaint of epigastric pain and generalized pruritus. He had had recurrent attacks of upper abdominal pain of many years' duration. These followed the ingestion of food of any type and remained localized to the upper abdomen, with radiation into the back. In May, 1949, he had been admitted to the hospital with the clinical picture of an abdominal catastrophe. A perforating duodenal ulcer was found and closed at exploratory laparotomy. Jaundice became evident two weeks following operation and was progressive until the time of his present admission.

The only significant physical signs were enlargement of the liver and epigastric tenderness. The blood count and urinalysis showed no significant abnormality, aside from the presence of bile in the urine. The bilirubin was 11.8 mg. per 100 cc. The van den Bergh test gave a direct positive reaction. Alkaline phosphatase was 6.1 units, and the thymol turbidity 7.0 units, per 100 cc. A roentgenogram of the upper gastrointestinal tract showed some scarring of the duodenal cap; no ulceration was noted.

On Sept. 12, 1949, an exploratory laparotomy was done and chronic fibrosing pancreatitis was found. Exploration of the common duct showed a diffuse stenosis in its pancreatic portion (Fig. 1). This lesion could not be differentiated from pancreatic carcinoma. Carcinoma was suspected on rapid study of a biopsy specimen from the pancreas. A pancreatoduodenectomy was done with an end-to-end choledochojejunostomy, and a Roux-Y jejunojejunostomy was completed. The cut end of the pancreas was buttressed against the side of the jejunum; the pancreatic duct was anastomosed to the jejunal mucosa over a no. 8 soft rubber catheter. The catheter was brought down the jejunal limb by the method described by Allen [10] for choledochojejunostomy.

The patient had an uneventful postoperative course. The final histologic diagnosis was duodenal ulcer with perforation into the pancreas, chronic pancreatitis, and obstruction of the common bile duct. The patient has remained well to the present, with the exception of an admission to the hospital in April, 1950, for repair of a right indirect inguinal hernia. He has remained in good nutrition; there is no demonstrable abnormality of function of the gastrointestinal tract and no abnormality of glucose metabolism.

---

8. Bowers, R. F., and Greenfield, J.: Choledochojejunostomy: Its Role in the Treatment of Chronic Pancreatitis, Ann. Surg. **134**:99-103 (July) 1951.

9. Longmire, W. P., and Briggs, J. D.: The Surgical Treatment of Pancreatitis, Am. Surgeon **18**:554-564 (June) 1952.

10. Allen, A. W.: A Method of Re-Establishing Continuity Between the Bile Ducts and the Gastro-Intestinal Tract, Ann. Surg. **121**:412-424 (April) 1945.

Comment.—This case indicates the difficulty of the operative differentiation of recurrent pancreatitis and carcinoma. Such difficulty has been generally experienced. The end-to-end choledochojejunestomy and the pancreatic duct-jejunal anastomosis have apparently functioned well. The patient has been completely relieved of all symptoms suggestive of recurrent pancreatitis, though final histologic examination of the tissue proved an operation of undue extent was done. There has been no evidence of biliary or pancreatic obstruction since operation. The use of a defunctionalized limb of jejunum to reestablish the continuity of the biliary tract and intestine has been entirely satisfactory.

CASE 2 (Pennsylvania Hospital Record No. 87560).—A 37-year-old Negro man was admitted to the Pennsylvania Hospital Nov. 4, 1949. His complaints upon admission were upper abdominal

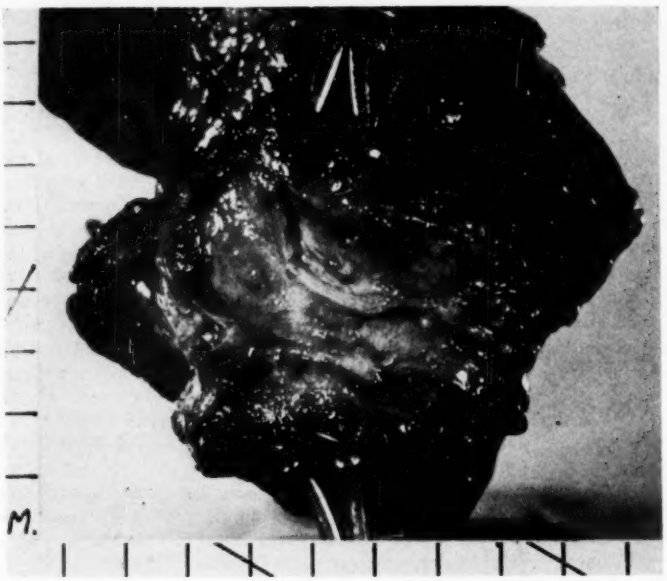

Fig. 1 (Case 1).—Photograph of opened pancreatic portion of common bile duct. There is progressive concentric narrowing of the duct in its passage through the pancreas. A probe of 1 mm. diameter would not pass through the duct at operation.

pain, recurrent chills, and fever. Symptoms started in 1938, when he was first hospitalized with severe recurrent epigastric pain. At that time the only significant finding was a small duodenal ulcer shown on the roentgenogram of the gastrointestinal tract. Treatment was with the usual medical regimen.

He was again admitted to the hospital in Sept. 1941, with the clinical picture of an abdominal catastrophe. Exploratory laparotomy was done, with a preoperative diagnosis of a perforating duodenal ulcer. The operative diagnosis was acute pancreatitis. He had an uneventful postoperative course and was discharged from the hospital.

After discharge, he had recurrent attacks of severe upper abdominal pain which were recognized as a sign of recurrent pancreatitis. Numerous amylase determinations showed a persistent elevation.

In July, 1949, he was again admitted to the hospital with upper abdominal pain and jaundice. The serum bilirubin was elevated; duodenal drainage revealed both calcium bilirubinate and cholesterol crystals in the duodenal contents. A roentgenogram showed "milk of calcium" in the

gall bladder and several calcified densities to the right of the third lumbar vertebra near the transverse process (Fig. 2). These areas of calcification had not been shown on previous abdominal roentgenograms. Exploratory laparotomy was done. Stenosing pancreatitis and chronic calculus cholecystitis were found. Exploration of the common duct revealed diffuse narrowing of the duct throughout the pancreatic portion. It was impossible to pass any instrument through the pancreatic portion of the gland. The head of the pancreas was extremely hard. The gall bladder was not removed; a tube drain was placed in the gall bladder and in the common duct above its pancreatic portion. The patient had an uneventful postoperative course, but his condition was improved. Jaundice, recurrent attacks of upper abdominal pain, chills, and fever persisted.

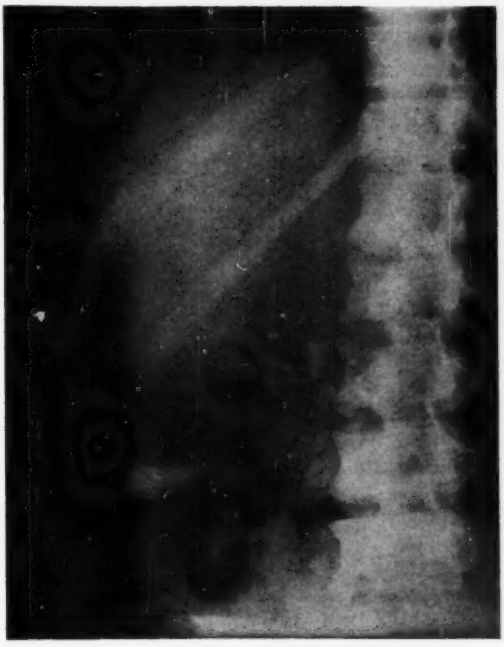

Fig. 2 (Case 2).—Calcium deposition in the pancreas secondary to recurrent acute pancreatitis. "Milk of calcium" is present in the gall bladder.

When admitted to the hospital for the fourth time, he appeared chronically ill. There were multiple draining sinuses in the right upper abdominal quadrant, with a T-tube extending from the common duct. A cholangiogram done on Nov. 5, 1949, showed almost complete stenosis of the pancreatic portion of the common duct (Fig. 3). The bilirubin was reported as 2.9 mg. per 100 cc., although the T-tube was functioning. The tolerance curve was of diabetic type. On Dec. 9, 1949, exploratory laparotomy was again performed. A hard, finely nodular pancreas was found. Cholecystectomy was done. End-to-side choledochojejunostomy, with a Roux-Y jejunojejunostomy, was done by the method of Allen. The patient had an uneventful postoperative course and was discharged from the hospital Jan. 3, 1950. He was asymptomatic and has remained free of symptoms to the present.

Comment.—This history is rather typical of the chronic illness produced by recurrent pancreatitis. The numerous operations had been unsuccessful in obtaining a satisfactory result, until internal decompression of the biliary tract was accom-

plished by choledochojejunostomy. Although a side vent was established above the pancreatic portion of the common duct rather than a complete by-pass of the "common channel," it has served to abolish recurrent pancreatitis completely. The Roux-Y jejunojejunostomy with a jejunal limb of adequate length has proved entirely satisfactory.

CASE 3 (Pennsylvania Hospital Record No. 78477).—This 51-year-old white woman was admitted to the Pennsylvania Hospital March 28, 1951. Her chief complaint on admission was recurrent upper abdominal pain. Attacks of severe abdominal and epigastric pain had recurred for 20 years. During this period she had consulted numerous physicians; extensive

Fig. 3 (Case 2).—Cholangiogram demonstrating complete obstruction of intrapancreatic portion of common duct secondary to stenosing pancreatitis.

and thorough diagnostic procedures had been utilized. However, a definite diagnosis had not been established, nor had any treatment recommended provided relief, until an exploratory laparotomy was done on March 5, 1947. A diagnosis of acute pancreatitis with extensive fat necrosis was established. Only drainage of the peripancreatic area was done. An extremely stormy postoperative course was complicated by extensive wound infection and a prolonged period of drainage from intraperitoneal suppuration. Recurrent attacks of upper abdominal pain continued.

In May, 1947, clinical jaundice occurred, associated with chills and fever. A laparotomy was again done; a peritoneal and pancreatic abscess was drained. After this, recurrent attacks of upper abdominal pain continued until the present admission.

Preceding her admission, she had had recurrent jaundice, chills, and fever associated with upper abdominal pain. The only significant physical findings on admission were an incisional

hernia in the right upper abdominal quadrant at the site of the previous operative procedures and epigastric tenderness. There was no significant abnormality of the blood count; the urine showed bile to be present. The serum bilirubin was 2 mg. per 100 cc.; the van den Bergh test gave a direct positive reaction. Serum alkaline phophatase was 8.4 units, and serum amylase was 60 mg., per 100 cc.

In April, 1951, exploratory laparotomy was done. The pancreas was hard and nodular; the gall bladder appeared to be normal; the common duct was greatly dilated. The common duct was explored. Narrowing of the entire pancreatic portion of the common duct prevented the passage of any instrument into the duodenum. Because the gall bladder and cystic duct appeared to be normal, the fundus of the gall bladder was anastomosed to the end of a defunctionalized limb of jejunum. A Roux-Y type jejunojejunostomy was performed.

The patient had an uneventful postoperative course and was discharged from the hospital on the 14th day after operation. After her discharge from the hospital she had recurrent chills and fever for three months. She was admitted to another hospital and given various antibiotics without effect. The attacks ceased spontaneously after this period; no further symptoms have occurred. At present she is completely asymptomatic; for the first time in many years she is free of pain; there are no significant physical findings.

Comment.—This history again demonstrates obstruction of the pancreatic portion of the common duct secondary to the fibrosis following recurrent attacks of acute pancreatitis. A different method of by-passing the terminal portion of the bile duct was used in this instance, and, though the immediate postoperative results seemed questionable, the eventual outcome has been entirely satisfactory.

Case 4 (Pennsylvania Hospital Record No. 94235).—A 69-year-old Negro man was admitted to the Pennsylvania Hospital with a chief complaint of upper abdominal and epigastric pain. This man had had his first onset of abdominal pain three years preceding admission, and since that time had had recurrent attacks which were associated with the ingestion of any type food.

He had been admitted to the hospital on one previous occasion in April, 1951; enlargement of the liver, distention of the gall bladder, and evidence of generalized jaundice were noted at that time. The significant laboratory findings were 7.2 mg. of bilirubin per 100 cc. and a direct positive van den Bergh reaction. Serum amylase was 88 mg. per 100 cc. An exploratory operation was done in June, 1951, and a fibrosing pancreatitis was found. No stones were in the gall bladder or the common duct. There was obstruction of the common duct in its panceatic portion. A loop cholecystojejunostomy was done without a proximal jejunojejunostomy. After this procedure, the jaundice improved, and the patient was discharged from the hospital.

He was readmitted to the hospital in March, 1952, with a history of continued epigastric pain, recurrent chills, and fever. There were no significant physical findings. No jaundice was present on this admission. Because of continued pain, intermittent chills, and fever, an exploratory laparotomy was done May 20, 1952. This patient was seen in consultation. It was recommended that the loop cholecystojejunostomy be replaced by a choledochojejunostomy with a Roux-Y jejunojejunostomy. This operation was done by Dr. Joseph Hoeffel. The pancreas was found to be densely indurated throughout its entire length. The common duct was greatly dilated and completely obstructed in its pancreatic portion. A cholecystectomy was done. The common duct was divided above the pancreatic portion. End-to-end choledochojejunostomy, with a Roux-Y jejunojejunostomy was performed. The patient had an uneventful postoperative course and was discharged from the hospital asymptomatic June 13, 1952.

However, he was readmitted to the hospital in Sept. 1952, with symptoms of duodenal obstruction. The patient was operated on again Sept. 20. There was gross evidence of neoplastic involvement of the pancreas. Biopsy of several masses about the pancreas was done; the histologic report was adenocarcinoma of the pancreas. After this, the patient's condition went rapidly downhill, and he died on Nov. 17, 1952; signs of carcinomatosis were present.

Comment.—This case report again illustrates the difficulty in the differentiation of fibrosing pancreatitis and carcinoma of the pancreas. It also illustrates the complications that can be expected to occur with a loop cholecystojejunostomy. It has

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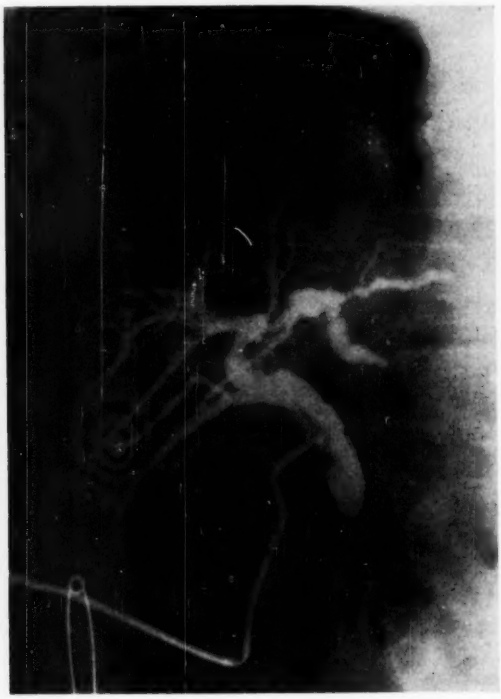

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been repeatedly demonstrated that in order to drain the biliary tree into the gastrointestinal tract it is necessary to use a defunctionalized limb of the jejunum to avoid cholangitis. After a proper type of internal biliary drainage was established, there were no further symptoms suggesting infection of the biliary tract. The benefits obtained by the biliary-intestinal anastomosis were short-lived because of the nature of the primary lesion. The initial symptoms and gross signs were those of pancreatitis. The eventual histologic changes were typical of adenocarcinoma of the pancreas. The duration of symptoms preceding hospital admission suggests the possibility that the initial symptoms were secondary to pancreatitis.

Case 5, (Germantown Hospital Dispensary Record No. 89689[11]).—This 27-year-old white man was admitted to the Germantown Hospital April 22, 1952, with the chief complaint of recurrent severe upper abdominal pain. The symptoms started three years preceding admission, and the pain had recurred at intervals of three to four months since the onset. He had had previous admission to the hospital Aug. 14, 1951, at which time a diagnosis of duodenal ulcer and pancreatic calcification was established. A cholecystogram done on this admission had shown some impairment of concentration of the dye in the gall bladder, but no calculi could be seen. He was discharged from the hospital with the recommendation for conservative treatment.

He had a second hospital admission in Oct., 1951, with the same symptoms, but for treatment of a pneumothorax which had occurred secondarily to a splanchnic injection of procaine for attempted relief of pancreatic pain. The lung promptly expanded.

In Nov., 1951, he was again admitted to the hospital with the same symptoms. Because of increasing frequency and severity of the upper abdominal pain, left thoracic sympathectomy and splanchnicectomy were done. The sympathetic chain from the third thoracic to the first lumbar segment was removed at this time, and all intrathoracic splanchnic nerves were excised with the sympathetic chain. He had immediate relief of his symptoms.

However, by Jan., 1952, there had been some recurrence of the upper abdominal pain, and this had increased in frequency and severity until the admission of April, 1952. The only significant fact in his past medical history was a spontaneous perforation of the gall bladder with biliary peritonitis that had occurred when the patient was 7 years of age. A laparotomy was done at this time, with closure of the perforation of the gall bladder.

The physical examination at the present admission disclosed no significant findings aside from the operative scars, which appeared to be well healed. A roentgenogram of the abdomen showed an increase in the amount of calcium deposition in the area of the pancreas when compared with the films of the previous admission. The gall bladder again was normal on roentgenography by the Graham-Cole method. The serum amylase values had been persistently normal on the previous and present admissions. The patient had been admitted to the hospital for total pancreatectomy. It was suggested that choledochojejunostomy be used as a substitute procedure. This was done by Dr. Joseph Stayman on April 25, 1952.

The pancreas was found to be edematous, hard and calcified. The common duct was grossly enlarged. A cholangiogram during the operation showed narrowing of the entire pancreatic portion of the common duct. The duodenum was then opened, the ampulla was located, and a small catheter was passed through the ampulla into the pancreatic duct. Roentgenograms then showed considerable calcification along the duct, but there was no obstruction. An end-to-end choledochojejunostomy, with an end-to-side Roux-Y jejunojejunostomy, was done. The gall bladder was removed. The patient had an uneventful postoperative course and was discharged from the hospital on the eighth postoperative day. Since his discharge from the hospital, he has been completely free of symptoms attributable to the pancreas and is working regularly.

Comment.—The history of spontaneous perforation of the gall bladder would suggest the possibility of obstruction to the outflow of the biliary tract during childhood. At no time in this patient's history was there any indication of calculus obstruction, and it is suggested that the obstruction was on the basis of spasm of the ampulla of Vater. This condition eventually resulted in diffuse pancreatitis, with

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extensive destruction of the pancreas manifested by generalized calcification. Left thoracolumbar sympathectomy and splanchnicectomy gave only temporary relief of symptoms. There was roentgenographic evidence of progressive calcification of the pancreas. Obstruction of the distal portion of the common duct was found at operation, secondary to the stenosing pancreatitis. Again, the venting of the unobstructed portion of the common duct into a defunctionalized limb of jejunum has relieved all symptoms. Examination of the stools has shown a moderate increase in fat which has persisted to the present. There has been no indication that the glucose metabolism has become abnormal. It is possible that had the functional obstruction of the common biliary and pancreatic drainage system been relieved at an earlier date the continued destruction of the pancreatic tissue would have been averted.

COMMENT

A surgeon confronted with the problem of the reestablishment of a satisfactory biliary-intestinal drainage tract following traumatic injury interrupts the continuity of the biliary drainage tract only with trepidation. Reconstitution of the biliary-intestinal continuity following trauma usually must be accomplished with scarred tissues, with grossly distorted anatomical relationships, and with a biliary tract which has generally been decompressed over a long period of time. The establishment of a common duct-jejunal anastomosis is not a difficult technical procedure when the tissues have minimal scarring and the common bile duct has been dilated by prolonged obstruction from an extraluminal source. In no instance has there been either leakage or evidence of stricture following the anastomosis. The production of a biliary-intestinal fistula above the site of obstruction of the common duct secondary to stenosing pancreatitis would seem a logical procedure. The decompression of the biliary tract either by sphincterotomy or by choledochojejunostomy has seemed to be effective in controlling recurrent pancreatitis. Division of the sphincter of Oddi has the advantage of relative technical simplicity and the maintenance of normal anatomical relationships. Extensive trial has proved it to be effective with but few exceptions. The divided sphincter may again become competent as healing and fibrosis occur. The results at present would not indicate that this occurs. Compared with sphincterotomy, choledochojejunostomy is a more difficult technical procedure, and normal anatomical relationships are distorted. The use of a defunctionalized limb of jejunum by the Roux-Y jejunojejunostomy has largely eliminated the danger of ascending infection in the biliary tract when the anastomosis is properly done. Each is a useful and applicable procedure.

The treatment of recurrent pancreatitis should stop the progress of the disease, as well as relieve the symptoms that are produced by the progressive disease. Progressive disease will result in sufficient tissue destruction that both external and internal secretory function of the pancreas are demonstrably impaired. Fibrotic replacement of destroyed pancreatic tissue may progress until stenosis of the pancreatic portion of the common bile duct occurs. Thereafter decompression of the common bile duct by end-to-end choledochojejunostomy is a logical and practical procedure for terminating the progress of the disease, as well as relieving symptoms. In the illustrative cases other types of anastomsis for decompression of the common bile duct have also been effective, provided a defunctionalized limb of the jejunum is used for anastomosis between the biliary and the gastrointestinal tracts.

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SUMMARY

A rational plan of procedure in cases of recurrent pancreatitis would seem to be the initiation of treatment by the division of the sphincter of Oddi at an early date in the disease. If the disease has progressed to the extent of stenosing pancreatitis, the anastomosis of the biliary tree to a defunctionalized limb of the jejunum on the hepatic side of the obstruction would seem to offer relief from the symptoms of pancreatitis and to stop the progress of the disease. This has been the experience in the five cases described herein. However, because of the recurrent nature of the disease, a longer time will be required before both procedures can be fully evaluated.

ABSTRACT OF DISCUSSION

Dr. John H. Mulholland, New York: Investigations of recurring pancreatitis have been going on for a number of years in the Department of Surgery, New York University College of Medicine, under the leadership of Dr. Henry Doubilet.

I agree with Dr. Allbritten that the commonest etiological factor in pancreatitis is diversion of bile into pancreatic ducts through a passageway between the common bile duct and the main pancreatic duct proximal to the sphincter of Oddi. Although my colleagues and I have seen jaundice accompany an acute attack of pancreatitis, this has generally been relieved with the subsidence of inflammation. The distressing persistent jaundice which occurred in Dr. Allbritten's cases is rare. He assumes that obstruction to the bile duct is produced by a stenosing fibrosis of the diseased pancreas; I would suggest another possibility. During the acute process we know that activated tryptic enzymes may ascend the bile ducts and be recovered in the acutely inflamed gall bladder. Perhaps such destructive enzymes did actually injure the lower common duct.

The problem posed by Dr. Allbritten's 1st and 4th cases—differentiation between chronic fibrosis or cirrhosis of the pancreas and carcinoma— has bothered us considerably. In one of our patients for whom diagnosis of pancreatitis was made, a sphincter section was performed with relief of symptoms, but eight months later operation revealed a widespread carcinoma arising from the body of the pancreas. This tumor was undoubtedly present at the first operation and was missed. The almost insurmountable difficulty involved in selecting the proper site for biopsy in a diffusely fibrosed pancreas has made us skeptical regarding the value of a negative report on a frozen biopsy section.

When area lymph nodes are enlarged, the immediate diagnosis is easier but such extension makes the prognosis, should it be carcinoma, hopeless. Resections for benign disease have been performed under the impression that the disease is malignant, but in a somewhat consoling fashion the reverse—a palliative procedure for what is believed to be carcinoma—occasionally results in complete recovery because the disease is benign, and the palliative procedure is generally an operation which by-passes the sphincter of Oddi.

We believe that section of the sphincter is the most direct approach to the relief of this disease. Anastomosis of the biliary tract to the bowel, or even simple T-tube drainage, will decrease biliary duct pressure which is created by spasm of the sphincter of Oddi and prevent further diversion of bile into the pancreatic ducts. In those patients with obliteration or destruction of the lower portion of the common duct, some by-passing procedure must be done, and Dr. Allbritten is to be congratulated on his success in this series. We have not seen such cases, but if we should, the experience cited here would guide us. I daresay if Dr. Allbritten's patients were operated on earlier in the course of their disease and simple sphincterotomy performed, the permanent obstruction in the lower bile duct might not have occurred.

Dr. Jonathan E. Rhoads, Philadelphia: Dr. Allbritten has introduced a new viewpoint into the discussion on treatment of chronic relapsing pancreatitis. For many years, this condition largely went untreated, unless calculi were present. Then an attempt was made to remove the calculi from the duct of Wirsung. Or if jaundice developed, the condition was often diagnosed at the time of operation as pancreatic carcinoma and treated by a cholecystojejunostomy or some other shunting procedure.

One of the early attempts to do something more definite for the relief of these patients was published by Rienhoff and Baker, who reported a case in which they had done a vagotomy and bilateral sympathectomy. This experience was rapidly followed by that of several other authors,

who found that sympathectomy alone frequently relieved symptoms and that in some instances only right sympathectomy was required. As this type of operation does not cure the pancreatitis, some authors went so far as to do a total pancreatectomy, which, of course, left the patients diabetic, even if they were not diabetic before the operation. Various procedures aimed at preventing a build-up of pressure in the pancreatic duct were advocated.

Doubilet and Mulholland proposed section of the sphincter of Oddi, at first, with a knife made to operate through the common duct and, later, under direct vision transduodenally. Cattell proposed anastomosing the dilated duct to a defunctionalized loop of small bowel and reported remarkable relief of pain in certain cases of pancreatic carcinoma.

Rienhoff proposed yet another approach when he suggested closing the ducts of Wirsung and of Sanatorini and ligating them. The thought was that the acinar tissue would then atrophy, leaving the islet tissue in a functioning state.

Usually, when a large number of methods are in use for the treatment of a condition, none of them is satisfactory. The treatment of chronic relapsing pancreatitis is an exception to this. We have had a good result with total pancreatectomy. We have had several good results with bilateral sympathectomy, and some patients seem to have been improved by sphincterotomy.

Dr. Allbritten has reported excellent relief in five patients in whom the common bile duct, and not the pancreatic duct, was decompressed. Not only is this method of treatment of value as a means for symptomatic relief in patients with this distressing condition but it is also of value from a theoretical standpoint.

If free drainage of the pancreatic duct does regularly relieve the symptoms of chronic relapsing pancreatitis, it strongly suggests that these symptoms are indeed related to periods when bile refluxes into the pancreas because of obstruction or spasm of the sphincter at the lower end of the common duct. Conceivably, the mechanism might be less simple; increase in pressure in the bile duct perhaps changes the flora of the biliary tract lymphatics, which, in turn, exposes the pancreas, via the pancreatic lymphatics, to bacterial insult.

Clearly, Dr. Allbritten's observations are of great interest and must be taken into account in any thinking we do regarding the etiology of the symptoms of chronic relapsing pancreatitis.

SUMMARY

A rational plan of procedure in cases of recurrent pancreatitis would seem to be the initiation of treatment by the division of the sphincter of Oddi at an early date in the disease. If the disease has progressed to the extent of stenosing pancreatitis, the anastomosis of the biliary tree to a defunctionalized limb of the jejunum on the hepatic side of the obstruction would seem to offer relief from the symptoms of pancreatitis and to stop the progress of the disease. This has been the experience in the five cases described herein. However, because of the recurrent nature of the disease, a longer time will be required before both procedures can be fully evaluated.

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I agree with Dr. Allbritten that the commonest etiological factor in pancreatitis is diversion of bile into pancreatic ducts through a passageway between the common bile duct and the main pancreatic duct proximal to the sphincter of Oddi. Although my colleagues and I have seen jaundice accompany an acute attack of pancreatitis, this has generally been relieved with the subsidence of inflammation. The distressing persistent jaundice which occurred in Dr. Allbritten's cases is rare. He assumes that obstruction to the bile duct is produced by a stenosing fibrosis of the diseased pancreas; I would suggest another possibility. During the acute process we know that activated tryptic enzymes may ascend the bile ducts and be recovered in the acutely inflamed gall bladder. Perhaps such destructive enzymes did actually injure the lower common duct.

The problem posed by Dr. Allbritten's 1st and 4th cases—differentiation between chronic fibrosis or cirrhosis of the pancreas and carcinoma— has bothered us considerably. In one of our patients for whom diagnosis of pancreatitis was made, a sphincter section was performed with relief of symptoms, but eight months later operation revealed a widespread carcinoma arising from the body of the pancreas. This tumor was undoubtedly present at the first operation and was missed. The almost insurmountable difficulty involved in selecting the proper site for biopsy in a diffusely fibrosed pancreas has made us skeptical regarding the value of a negative report on a frozen biopsy section.

When area lymph nodes are enlarged, the immediate diagnosis is easier but such extension makes the prognosis, should it be carcinoma, hopeless. Resections for benign disease have been performed under the impression that the disease is malignant, but in a somewhat consoling fashion the reverse—a palliative procedure for what is believed to be carcinoma—occasionally results in complete recovery because the disease is benign, and the palliative procedure is generally an operation which by-passes the sphincter of Oddi.

We believe that section of the sphincter is the most direct approach to the relief of this disease. Anastomosis of the biliary tract to the bowel, or even simple T-tube drainage, will decrease biliary duct pressure which is created by spasm of the sphincter of Oddi and prevent further diversion of bile into the pancreatic ducts. In those patients with obliteration or destruction of the lower portion of the common duct, some by-passing procedure must be done, and Dr. Allbritten is to be congratulated on his success in this series. We have not seen such cases, but if we should, the experience cited here would guide us. I daresay if Dr. Allbritten's patients were operated on earlier in the course of their disease and simple sphincterotomy performed, the permanent obstruction in the lower bile duct might not have occurred.

DR. JONATHAN E. RHOADS, Philadelphia: Dr. Allbritten has introduced a new viewpoint into the discussion on treatment of chronic relapsing pancreatitis. For many years, this condition largely went untreated, unless calculi were present. Then an attempt was made to remove the calculi from the duct of Wirsung. Or if jaundice developed, the condition was often diagnosed at the time of operation as pancreatic carcinoma and treated by a cholecystojejunostomy or some other shunting procedure.

One of the early attempts to do something more definite for the relief of these patients was published by Rienhoff and Baker, who reported a case in which they had done a vagotomy and bilateral sympathectomy. This experience was rapidly followed by that of several other authors,

who found that sympathectomy alone frequently relieved symptoms and that in some instances only right sympathectomy was required. As this type of operation does not cure the pancreatitis, some authors went so far as to do a total pancreatectomy, which, of course, left the patients diabetic, even if they were not diabetic before the operation. Various procedures aimed at preventing a build-up of pressure in the pancreatic duct were advocated.

Doubilet and Mulholland proposed section of the sphincter of Oddi, at first, with a knife made to operate through the common duct and, later, under direct vision transduodenally. Cattell proposed anastomosing the dilated duct to a defunctionalized loop of small bowel and reported remarkable relief of pain in certain cases of pancreatic carcinoma.

Rienhoff proposed yet another approach when he suggested closing the ducts of Wirsung and of Sanatorini and ligating them. The thought was that the acinar tissue would then atrophy, leaving the islet tissue in a functioning state.

Usually, when a large number of methods are in use for the treatment of a condition, none of them is satisfactory. The treatment of chronic relapsing pancreatitis is an exception to this. We have had a good result with total pancreatectomy. We have had several good results with bilateral sympathectomy, and some patients seem to have been improved by sphincterotomy.

Dr. Allbritten has reported excellent relief in five patients in whom the common bile duct, and not the pancreatic duct, was decompressed. Not only is this method of treatment of value as a means for symptomatic relief in patients with this distressing condition but it is also of value from a theoretical standpoint.

If free drainage of the pancreatic duct does regularly relieve the symptoms of chronic relapsing pancreatitis, it strongly suggests that these symptoms are indeed related to periods when bile refluxes into the pancreas because of obstruction or spasm of the sphincter at the lower end of the common duct. Conceivably, the mechanism might be less simple; increase in pressure in the bile duct perhaps changes the flora of the biliary tract lymphatics, which, in turn, exposes the pancreas, via the pancreatic lymphatics, to bacterial insult.

Clearly, Dr. Allbritten's observations are of great interest and must be taken into account in any thinking we do regarding the etiology of the symptoms of chronic relapsing pancreatitis.

SURGICAL TREATMENT OF MITRAL STENOSIS

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SURGICAL relief of mitral obstruction may now be said to have become an established practice. In sharp contrast to the insurmountable difficulties which beset the attempts to apply this form of therapy in the 1920's, current procedures have the advantage of advances in surgical technique, in anesthetization, in preoperative and postoperative care, and in the control of infection with chemotherapy and antibiotics. Furthermore, it is now possible, with techniques of cardiac catheterization and tests of circulatory and pulmonary function, to appraise, in more or less quantitative terms, the physiological changes consequent upon the obstruction at the mitral valve. Finally, changes in pressure in the pulmonary circulation and even in the left auricle may also be checked at the time of operation. Not only have such measurements served to confirm deductions, based on symptoms and physical signs, with regard to the dynamic consequences of mitral stenosis, but they have demonstrated the variability of these data as well.

Although mitral stenosis is the dominant manifestation of a disease of the heart, these patients suffer from a disease of the lungs. The obstruction to flow through the mitral valve provokes retrogressive rise in pressure in the pulmonary veins and, most important, in the pulmonary capillaries, that critical portion of the pulmonary circulation where blood flow and ventilation collaborate in the function of respiration. When the hydraulic pressure in the pulmonary capillaries exceeds the oncotic pressure of the blood serum (at about 35 mm. of mercury), transudation of fluid takes place about the capillaries in the alveolar wall and into the alveoli themselves.

With mitral obstruction of significant degree, a striking rise often develops in the resistance to flow in the peripheral pulmonary arteries. While this resistance is no measure of the patient's disability, it has some significance at its extremes. Operative results are usually better when pulmonary arterial pressure is low in relation to pulmonary "capillary" pressure and are almost uniformly poor when pulmonary vascular resistance has become fixed at a high level. The mechanism whereby pulmonary arterial pressure is raised is still unclear; the anatomical changes in the pulmonary arterioles, occasionally described, are too infrequent and too widely scattered to account for the evidently serious impediment to blood flow.

Read in the Symposium on the Indications and Results of Surgical Treatment of Heart Disease before the joint meeting of the Section on Experimental Medicine and Therapeutics and the Section on Internal Medicine at the 102d Annual Meeting of the American Medical Association, New York, June 4, 1953.

The symptoms of which patients with mitral stenosis complain are the subjective consequences of these changes in the pulmonary circulation. Breathlessness, cough, pulmonary edema, and paroxysmal nocturnal dyspnea are closely related to pulmonary congestion, especially in the area of the pulmonary capillaries.

Hemoptysis, which may vary in degree from pink staining of the frothy edema fluid coughed up in such an attack to more evident blood streaking in the sputum in instances of pulmonary infarction, and even to frank and copious bleeding from the trachea, is likewise a consequence of blood stasis in the lungs. Of all types of hemoptysis, the last is the most serious. It represents rupture of submucosal varices in the bronchi, which develop in an evident attempt to provide a collateral vent from the engorged pulmonary veins to the azygos system.

Certain physical signs, too, depend on this dynamic back pressure. The increased pulmonary resistance raising the pressure in the main pulmonary arteries strikingly augments the intensity of the second pulmonic sound or may even provoke the murmur of relative pulmonic insufficiency. The load on the right ventricle may bring about right axis deviation in the electrocardiogram or the pattern of right ventricular "strain." When pulmonary resistance is high for long periods, or if the heart muscle itself is actively diseased by the rheumatic process, right heart failure may supervene, with relative tricuspid insufficiency, systemic venous congestion, and hepatic engorgement. These may yield to therapeutic measures, such as administration of digitalis and salt restriction; but, when the pulmonary resistance is fixed at a high level, intractable failure of the right side of the heart may occur.

The obvious need to break the dam causing this back pressure and its effects stimulated the trial of surgical treatment of mitral stenosis. Thousands of operations have now been performed in this country and abroad, and the results have been rewarding in a large percentage of the patients. At the same time, failures have occurred, apparently unavoidable complications have ensued, and, unhappily, early improvement has not endured in some instances.

This communication is offered less in the hope of presenting new advances in the subject than of describing the experience in one hospital with a carefully followed series of patients. It is based on the preoperative and postoperative observation of 75 patients, ranging in age from 20 to 49 years and including 17 men and 58 women. All survivors have been followed at least six months after operation.

There is now general agreement regarding the indications for operation: symptoms and signs of pulmonary engorgement, including dyspnea of a degree limiting the patient's activity and characteristically associated with cough, paroxysmal nocturnal dyspnea, attacks of pulmonary edema after exertion or at rest, and hemoptysis. These signs and symptoms formed the basis of selection in this series; their relative frequency is shown in Table 1.

With one exception,[1] all the characteristic signs of mitral stenosis were present in each of these patients: snapping accentuation of the first sound at the apex and of the second sound in the pulmonic area, and middiastolic or late diastolic rumbling murmur. In the electrocardiogram right axis deviation was commonly, though not

1. In this patient severe symptoms and signs of pulmonary congestion accompanied typical changes in cardiac contour, although the characteristic murmur was never heard. At operation tight mitral stenosis was discovered and relieved (Levine, S. A., and Love, D. E.; Mitral Stenosis Without Murmurs, Cardiologia **21**:599, 1952).

uniformly, recorded. The most helpful sign by fluoroscopy was enlargement of the proximal portion of the pulmonary artery and pulmonary conus, with or without enlargement of the left auricle. In what have proved to be the most favorable instances, evidence of pulmonary congestion was genuine, or even extreme, without x-ray evidence of conspicuous left auricular enlargement.

With regard to contraindications, bacterial endocarditis is the most obvious and, fortunately, the least frequent. Aortic valve disease needs to be carefully evaluated with regard to its probable influence in any given case upon the consequences of mitral valvotomy. The murmur of aortic insufficiency may in some instances be distinguished only with the greatest difficulty from that of pulmonic insufficiency. In several patients in this series, signs of aortic insufficiency persisted or even progressed after operation, although in some the possibility of confusion with pulmonic insufficiency still exists. When the deformity of the aortic valve produces any considerable degree of obstruction, it would seem likely to impair significantly the benefit that might otherwise be derived from relief of the mitral obstruction. In these circumstances, the impediment at the aortic orifice would possibly promote

TABLE 1.—*Frequency of Signs and Symptoms*

Signs and Symptoms		No. of Cases
Severe dyspnea with exertion (1-15 yr.)		75
Cough, few months to years		55
Hemoptysis		39
Severe and repeated	20	
Mild to moderate	19	
Pulmonary edema		30
Right-sided heart failure		28
Auricular fibrillation, established		26

regurgitation of blood back through the mitral valve during ventricular systole. In at least one patient in this series who died soon after operation, the degree of obstruction at the aortic orifice had been underestimated and precisely the conditions described above ensued.

Patients with intractable right heart failure constitute a special category. In our experience, mitral valvotomy in such patients has been relatively unrewarding and the mortality has been prohibitively high. These poor results may obviously be due to one or both of two factors, neither of which can be relieved by mitral valvotomy; the pulmonary vascular resistance may have become more or less irreversibly fixed at a high level, or, perhaps because of active myocardial disease, the muscle may have given way under the load.

Operation in the presence of active rheumatic disease in the myocardium is probably also a contraindication so far as it can be recognized. In this series every effort has been made to avoid operation in the presence of an elevated erythrocyte sedimentation rate. Even so, rheumatic carditis evidently was activated by operation or was active at the time surgery was undertaken in five patients. As soon as they are seen, all patients should be placed on sulfadiazine prophylaxis, if it has not already been initiated, and this should be reinstituted as soon as penicillin therapy is discontinued after operation.

In the selection of patients in this series for operation, commissurotomy was not advised for those in whom insufficiency was regarded as the dominant abnormality of the mitral valve. Obviously, the evaluation of the significance of mitral insufficiency is uncertain and difficult, but some signs proved helpful. This cannot be said of the pattern of disability, which was not peculiar to those patients with predominant insufficiency. Nor were the intensity of the murmur and the direction and extent of its transmission of distinctive value in this regard. More helpful was the quality of the first sound as affected by the murmur; when mitral stenosis is dominant, even though there is a clearly audible systolic murmur, the first sound has its characteristic sharp, intensified quality. On the contrary, with significant mitral insufficiency, the first sound at the apex is often blurred or obscured by the systolic murmur.

The localized forceful apex impulse, indicative of vigorous left ventricular contraction, is frequently encountered with dominant mitral insufficiency, and on fluoroscopic examination enlargement of the left ventricle is visible. Along with these changes in the ventricle, there occur frequently, but not invariably, changes in the electrical axis of the electrocardiogram. With "pure" or dominant mitral stenosis, right axis deviation or even the characteristic pattern of right heart "strain" is often seen. When the electrical axis is balanced in the normal fashion, mitral stenosis may still be present but may be complicated by significant mitral insufficiency; here the conclusion must be drawn from other signs. Less helpful information may be derived from the quality of the second pulmonic sound. In the genuinely disabled patient with "pure" mitral stenosis, the second pulmonic sound is loud and frequently reduplicated. In a fair proportion of patients with dominant mitral insufficiency, the second pulmonic sound is not impressively accentuated.

Enlargement of the left auricle tends to be exaggerated in patients with significant mitral insufficiency; indeed, some of the largest left auricles observed have been encountered in these patients. Paradoxical dilatation of the left auricle coincident with left ventricular systole may be demonstrated by slit kymography, but when this dilatation can be demonstrated, the other signs of dominant mitral insufficiency are usually impressive.

RESULTS

The operative results in this series are shown in Table 2.[2] They compare favorably with those reported in other larger series.[3] It has not yet proved possible to predict with confidence in every instance whether, barring misfortune, the operative result will be excellent, good, or only fair. Among those patients with no evidence of active rheumatic disease, with signs of "pure" mitral stenosis, and without significant cardiac enlargement, the consequences have usually been most rewarding.

2. In the two cases described as "failures," the left auricle could not be entered at operation, in one because of massive organized thrombus and in the other because of lack of auricular appendage and small pulmonary veins.

3. Harken, D. E.; Ellis, L. B.; Ware, P. F., and Norman, L. R.: Surgical Treatment of Mitral Stenosis: Valvuloplasty, New England J. Med. **239**:801, 1948. Bailey, C. P.: The Surgical Treatment of Mitral Stenosis: Mitral Commissurotomy, Chest Dis. **15**:377, 1949. Glover, R. P.; O'Neill, T. J. E., and Bailey, C. P.: Commissurotomy for Mitral Stenosis, Circulation **1**:329 1950. Baker, C.; Brock, R. C.; Campbell, M., and Wood, P.: Valvulotomy for Mitral Stenosis: Further Report on 100 Cases, Brit. M. J. **1**:1043, 1952.

Among patients in Group IV with most serious disability,[4] operation is always advised with grave misgivings, and, to those in the intermediate groups, it must often be recommended with reservations. However, since many patients in Group III and some in Group IV have been restored at least for the period of observation to a more comfortable and productive existence, surgical treatment has certainly earned a place even in these categories.

Particularly striking with regard to the postoperative results is the fact that improvement in the measurable alterations in pressure and flow in the pulmonary circulation and in the estimated pulmonary function by no means keeps pace with the subjective improvement noted by the patients or with their ability to carry out the physical activities of living.

The resting cardiac output is probably the least valuable datum in tracing the progress of these patients after surgical relief of mitral obstruction. Typical results are indicated in Chart 1 for a series of patients studied by cardiac catheterization before and up to 41 months after operation.[5] The changes are variable; in only two patients has the normal value (3.0 L. min./M.^{2}) been reached.

The mean pressure in the pulmonary artery estimated at rest, while it shows more pronounced changes after operation than does the resting cardiac output, has

TABLE 2.—*Results of Surgical Treatment of Mitral Stenosis*

	No. of Cases
Excellent result	34
Good result	17
Fair result	13
Failure	2
Death	9*

* Four patients died of embolism; four, of progressive cardiac failure, and one, of staphylococcic pericarditis.

fallen to normal (15 mm. of mercury) in only 2 of the 10 patients for whom data are shown in Chart 2. This pressure may diminish by as much as 30%, with a corresponding fall in left auricular pressure, immediately after the valve is opened at operation.

"Total pulmonary resistance,"[6] a calculation which relates pressure and flow in the pulmonary circuit and also serves to indicate the energy required of the right ventricle to accomplish pulmonary blood flow, is rather more consistently reduced after operation, but it is no clear measure of improvement (Chart 3).

It is one of the functional marks of mitral stenosis that, in contrast to the normal condition, the patient cannot increase cardiac output upon demand, e. g., with exercise, without extravagant rise in pulmonary artery pressure. Preoperative and

4. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association, 1940.

5. The preoperative observations and some of the early postoperative measurements were made by Dr. Richard Bing, the remainder by Drs. Henry Bahnson and Arthur Otis.

6. "Total pulmonary resistance" equals $PA \times 1332/CO$, where PA is mean pulmonary arterial pressure in millimeters of mercury; 1322 is the conversion factor from the millimeters of mercury to dynes per centimeter squared, and CO is cardiac output in cubic centimeters per second.

postoperative data on eight patients are presented in Chart 4. All patients represented were dramatically improved after operation, as tested by the stress of living, and three or four showed improvement in the function under consideration, but none reached the normal range.

With long-standing congestion of the lungs and sustained high pressure in the pulmonary capillaries, measurable deficiencies in respiratory function understandably occur. To the appraisal of these changes, Cohn, Riley, and Carroll [7] applied the estimation of diffusion capacity: the amount of oxygen diffusing from alveolar gas to alveolar capillary blood per minute per millimeter of mercury gradient partial

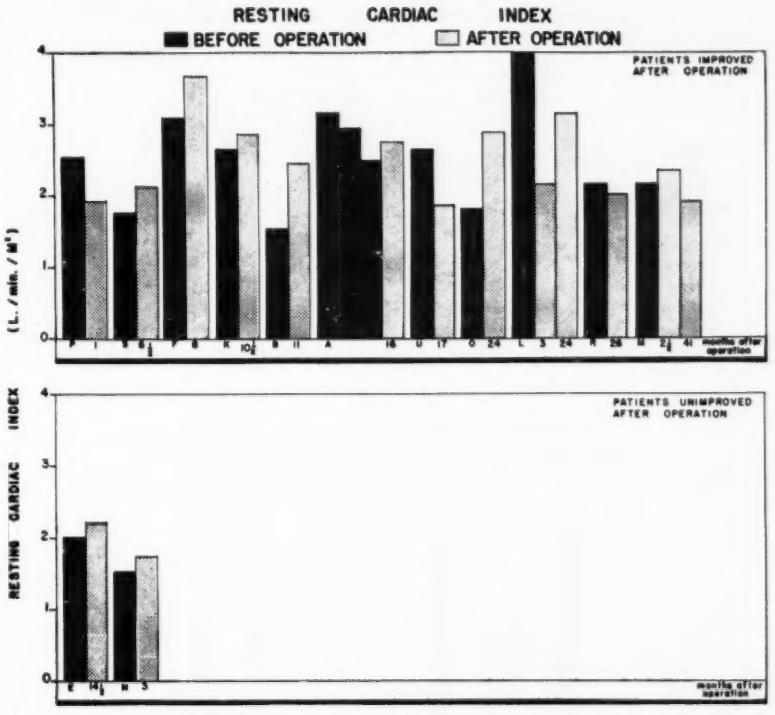

Chart 1.—In this chart and the two succeeding charts, letters at foot of columns denote patients, while numbers indicate months after operation.

pressure of oxygen. The diffusion capacity is obviously dependent on (*a*) the area of diffusing surface in the lungs—length, diameter, and number of alveolar capillaries—and (*b*) the permeability of each unit area. When this capacity can be determined during a steady state of exercise on a treadmill, a maximal, or nearly maximal, value is obtained. In these circumstances, presumably all available capillaries take part in gas exchange, and the maximal diffusion capacity reflects the condition of the entire diffusing surface of the lungs; thus, it becomes a structural as well as a functional concept.

7. Cohn, J.; Riley, R. L., and Carroll, D.: Pulmonary Function in Mitral Valvular Disease; Distribution and Diffusion Characteristics in Resting Patients, J. Clin. Invest., to be published.

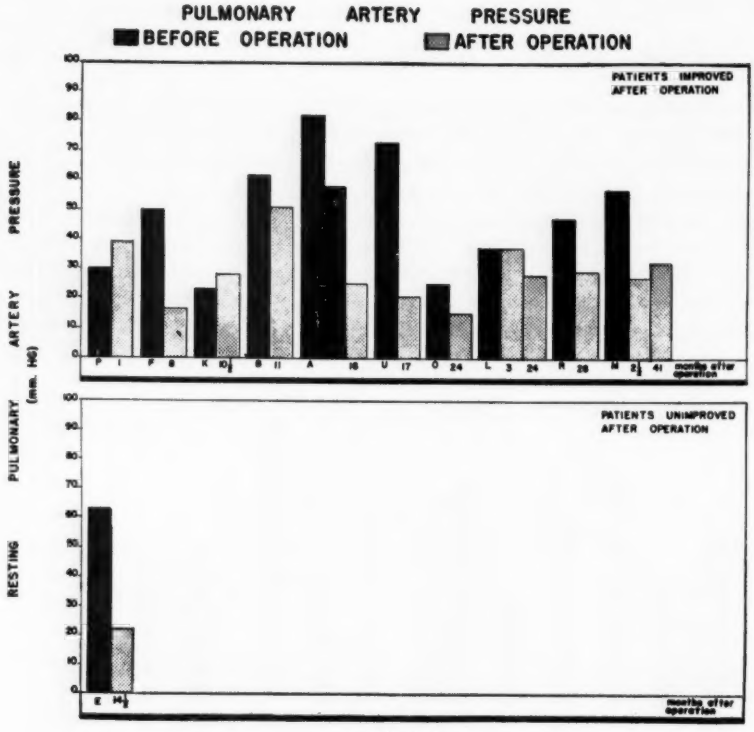

Chart 2.

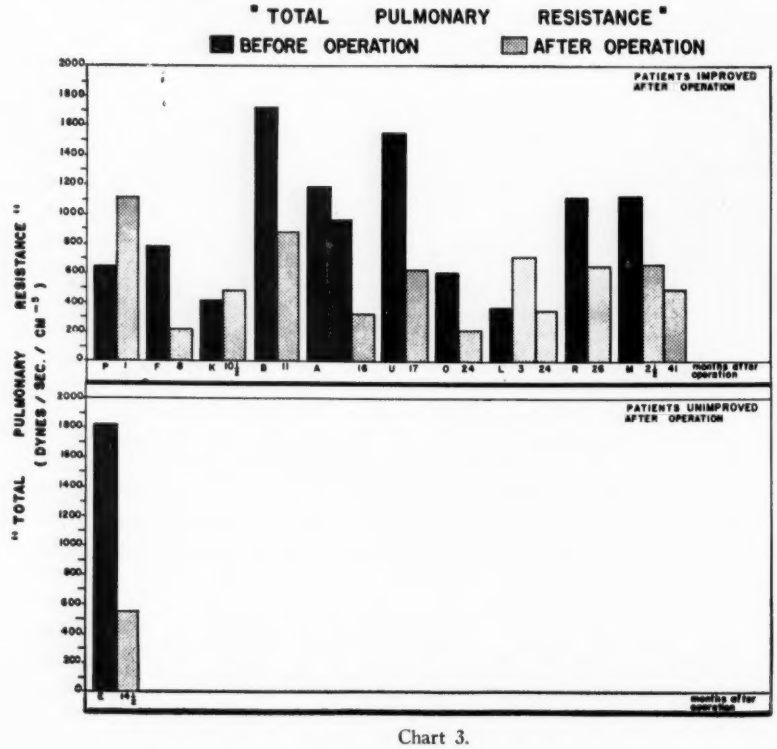
" TOTAL PULMONARY RESISTANCE "
BEFORE OPERATION
AFTER OPERATION
PATIENTS IMPROVED AFTER OPERATION
PATIENTS UNIMPROVED AFTER OPERATION
" TOTAL PULMONARY RESISTANCE " (DYNES / SEC. / CM⁻⁵)
months after operation

Chart 3.

Riley and his associates measured the maximal diffusion capacity in 15 patients of this series after operation. All these patients are now able to perform ordinary physical activity with no discomfort. In a few the maximal diffusion capacity is now normal or nearly so, but in the majority it is still significantly depressed.

The measured improvement in no one of these functions—pulmonary arterial pressure, cardiac output, total pulmonary resistance, and maximal diffusion capacity—fully describes the clinical improvement in these patients following valvotomy. Nevertheless, even with allowance for a considerable psychological reaction on the part of patients to this somewhat dramatic procedure, they are demonstrably more comfortable; orthopnea has disappeared; dyspnea has diminished or vanished, and

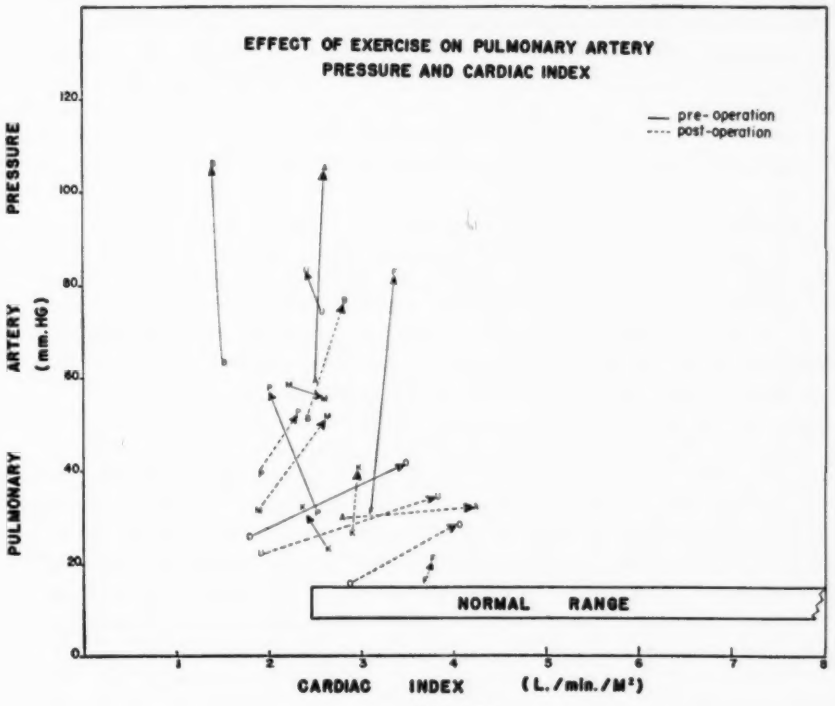

Chart 4.

other symptoms of pulmonary congestion have rapidly and progressively abated. These facts may be interpreted as indicating that the patient's ability to withstand the physical stress of living is probably a more comprehensive test than any others so far devised, possibly involving factors into which our functional studies do not yet precisely penetrate.

COMPLICATIONS

The two most significant complications are embolism and active rheumatic disease.

Embolism.—Embolism is most likely to occur, though it is not inevitable, in two groups of patients. The first is that group with advanced disease in whom the normal

sinus rhythm has been replaced by auricular fibrillation. In some, though by no means all, mural thrombi form in the auricle. These may be unsuspected until discovered or dislodged at operation, or the patient may give a clear history of one or more attacks of embolism in the past. Such a history is not an absolute contraindication to operation, though it certainly counsels caution, and operation should not, if avoidable, be performed within six months of the last embolic attack. We have not resorted to anticoagulant therapy in the face of these phenomena, and we hold the view that amputation of the auricular appendix in the hope of excising the site of origin of such emboli is not likely to be successful. Thrombi are found as well in the body of the atrium, and the stagnation of blood in that chamber, which presumably promotes formation of the mural thrombus, will not be reduced unless the mitral obstruction is concurrently relieved.

As experience has accumulated, it has become evident that there is a significant hazard of embolism during or shortly after mitral valvotomy in patients with densely calcified valve cusps. Fortunately, these patients are in the minority among those otherwise suitable for operation, but two of the most tragic accidents of this sort in our series occurred in patients with normal sinus rhythm but with densely calcified valves.

Fatal embolism occurred in four patients of this series. In three others, hemiplegia was present immediately after operation and cleared completely in two. Our surgical colleagues are better able to design means to avoid embolism in these circumstances. Occlusion of the main arteries to the head is recommended and practiced during certain critical maneuvers in this operation, e. g., when the finger is introduced into the auricle or, in the case of the calcified valve, when the actual fracture is performed, but such occlusions cannot be sustained for indefinite periods.

Active Rheumatic Heart Disease.—The careful study and long observation to which patients undergoing mitral surgery are subjected has brought new emphasis to the fact that rheumatic carditis is often a smoldering, intermittent, or recrudescent disease, and that it is not limited to persons in the early decades of life. Various groups [8] have described the discovery of typical Aschoff lesions in the portion of the auricular appendix removed at operation, and our own experience has been similar to theirs: "Characteristic" Aschoff bodies were present in 40 of 66 patients. Others have studied such patients by various means in order to discover the presence of active rheumatic fever, but the occurrence of such lesions in the heart evidently cannot be predicted from prior estimations of the antistreptolysin titer or the erythrocyte sedimentation rate. Neither the presence nor the absence of these lesions serves to predict the results of operation or the postoperative course. The small portion of the auricle removed at operation is obviously not a fair or adequate sample of the myocardium as a whole, and thus far the discovery of these lesions has been more puzzling than enlightening.

8. Ellis, L. B. and others: Studies in Mitral Stenosis: A Correlation of Physiologic and Clinical Findings, A. M. A. Arch. Int. Med. **88**:515, 1951. Kuchner, M., and Others: Rheumatic Carditis in Surgically Removed Auricular Appendages, Am. Heart J. **43**:286, 1952. Sabiston, D. C., Jr., and Follis, R. H., Jr.: Lesions in Auricular Appendages Removed at Operation for Mitral Stenosis of Presumed Rheumatic Origin, Bull. Johns Hopkins Hosp. **91**:178, 1952. Biörck, B.; Winblad, W., and Wulff, H. B.: Studies in Mitral Stenosis: Observations on Incidence of Active Rheumatic Carditis in Left Auricular Appendages Resected at Operation for Mitral Stenosis, Am. Heart J. **44**:325, 1952.

Five of the surviving patients in this series underwent evident reactivation of rheumatic heart disease within a short period following operation. These recrudescences were not preceded by overt respiratory infections, and they occurred despite the fact that the patients were constantly and vigorously treated with penicillin during the immediate postoperative course. In at least five others, respiratory infection brought about a worsening of symptoms and a progressive decline in work tolerance, even though the early consequences of operation had evidently been favorable.[9] Indeed, it is on the probability of recurrent rheumatic disease—a factor as yet unpredictable—that the persistence of benefit after operation will conceivably depend. This problem points urgently to the need for more careful attention to prophylaxis with sulfadiazine or penicillin in patients with rheumatic heart disease regardless of age.[10] Furthermore, it excites a special interest in the development of more informative tests to determine the presence of rheumatic activity and, above all, of more adequate therapy for this disease.

SUMMARY AND CONCLUSIONS

Surgical relief of mitral obstruction, now an established procedure, brought considerable and sometimes dramatic improvement to nearly three-fourths of a series of 75 patients selected because of genuine and progressive circulatory disability. Improvement has persisted in most of the patients followed three years or more.

Obviously, clinical improvement in these patients must depend on the improved ability to increase the flow of blood through the lungs with exertion, without causing congestion in the critical capillary area. The physiological measurements so far applicable during exercise do not serve adequately to explain the subjective betterment of these patients. The capacity to withstand the physical stress of living is still the most informative test in this regard.

The two most devastating complications are embolism at operation and reactivation of rheumatic carditis. The former is a surgical problem. The latter calls for the most thorough application of the only known methods of preventing rheumatic fever: prophylaxis against streptococcic infections of the respiratory tract with sulfadiazine or penicillin or, failing this, the prompt initiation of antibiotic therapy at the onset of the respiratory infection.

The need for surgcal relief of mitral stenosis is determined by rheumatic fever. The ultimate success of this procedure will likewise depend on the subsequent control of that disease.

ABSTRACT OF DISCUSSION

DR. ROBERT P. GLOVER, Philadelphia: [Slide] The first problem in the surgical treatment of mitral stenosis is when these patients should undergo operation. There is much discussion on this problem. For pathological reasons, my colleagues and I feel surgery should be performed early. Neither the cardiologists nor I feel that we should operate on patients with mitral stenosis who have merely a murmur. We are not operating to correct a murmur; we are operating to correct a function. At present, a murmur alone is not an indication, in our opinion. We feel, however, that the development of symptoms increasing pulmonary vascular pressure is an indication for operation. "One can recognize the early effects of rheumatic fever on the valve . . . along the cusp margins." As time goes on, the anterior and posterior leaflets become adherent at the commissures.

9. In one patient without overt signs of recurrent disease, symptoms and signs appeared which indicated that the valve orifice had again become critically narrowed.

10. Prevention of Rheumatic Fever, Mod. Concepts Cardiovas. Dis. **22**:158, 1953.

[Slide] The state of pronounced stenosis, early and late, is a pathological category. For the first few years, it is perhaps not associated with symptoms. But at what we call the critical level in the size of the mitral orifice, the heart can no longer compensate for the increasing stricture. Breakdown of the myocardium and of the entire vascular system begins. At that point, when the orifice is about the size of a fingertip or a cigaret, symptoms develop. Then the patient may report that he is a bit short of breath when climbing stairs. The physician may think that the disease is in an early stage, and indeed it is, from a symptomatic standpoint. But from a pathological standpoint, the disease is already in a late stage. Progression of the early symptoms does not mean the valve is becoming smaller. It is already as small as it will ever get. From this point on, the process heaps up and becomes thicker and more calcified. Why, then, should operation be put off until the patient has all the complications in the book? Why not operate when the valve is about as small as it is going to be, while it is still somewhat pliable?

[Slide] This slide shows the incidence of pleuropericardial pain after commissurotomy. An appreciable proportion, 30 to 40%, of the 500 patients now in our series showed signs of what we feel to be a smoldering reactivation of rheumatic fever. One may argue that these signs are an expression of atraumatic pericarditis. The condition is, in many instances, characterized by fleeting pain, sometimes mild and sometimes severe. It lasts three to six months, or longer, and appears intermittently. Frequently, it is accompanied with elevation in temperature to 101 or 102 F. Congestive failure also sometimes accompanies the condition. Although we lack a substantiating laboratory test, clinical experience suggests that this condition is a mild reactivation, in most instances, of a smoldering rheumatic state. After all, the operation is merely an incident in the course of the continuing care of the rheumatic patient.

In our first series of 164 cases, there were 2 cases of embolization. For the entire series to date, the rate is 2.5%, including both cerebral and peripheral embolism. Dr. Charles P. Bailey devised a method of avoiding cerebral embolism by occluding the clotted vessels. We have not used his method because in some respects it can be dangerous. The vessels may be traumatized, producing additional cerebral anoxia, with the occurrence of emboli anyway. We depend on careful manipulation and control of the appendage itself; however, there will always be a certain number of postoperative emboli.

[Slide] Thirty-four per cent of the appendages examined by our pathologists showed the presence of rheumatic activity. However, we find no correlation of rheumatic activity with the pericardial syndrome. This is reasonable, because one would not expect to find the major lodging place for stigma of rheumatic fever to be the tip of the appendage. If the entire heart could be examined in these cases, I am sure all would show signs of rheumatic fever.

[Slide] This patient died as a result of an automobile accident about a year and a half after operation. Results of the operation were excellent. The valve was opened widely and remained so. In our series we have not noticed the return of any stenotic process after surgery. A histologic view of this heart would show that the cusp margins have become endothelized, so that the stenotic process does not tend to return.

In many of these cases, one should use a knife along with the finger in the operation. If the commissure is not opened to the myocardium and a little fusion is left on the myocardium, the stenotic process may return. We think it is imperative in every instance to open the commissure to the myocardium—and the knife certainly helps us to do that.

[Slide] I want to warn you also that the patient does not obtain the full result of the operation immediately. He should be cautioned that he is not going to "take up his bed and walk" right out of the hospital. He should be told that six months to year of watching is necessary.

The data on catheterization in this slide show that for two years after operation pulmonary artery pressures continually decline, an indication of the adjustment to the new state.

[Slide] Results for our entire series have become fairly well stabilized. In 76% of the patients, the operation was worth while, and the patients' condition is either excellent or improved. Ten to 15% of the patients showed no improvement. Operative mortality to date is 5.9%, with the inevitable 5% of deaths occurring late after operation because of irreversible changes that progressed despite removal of the blocking dam.

DR. DWIGHT E. HARKEN, Boston: The problems of surgical treatment of mitral stenosis have been presented rather fully and with absolute accuracy. There cannot be much disagreement in regard to the facts.

The problem of acute rheumatic fever (rheumatic carditis) raised by Dr. Andrus is a great challenge in diagnostic preoperative evaluation. We seem to have gone about as far toward a solution as we can go. Dr. Glover showed that up to 40% of his series had what he called reactivation of rheumatic fever. That group can be divided further according to the presence of Aschoff bodies, if they are evidence of rheumatic activity. Paradoxically, the young patient without fibrillation is the most apt to have Aschoff bodies. In our patients under 35 years of age without fibrillation, 85% showed Aschoff bodies. However, in patients over 45 with fibrillation, the incidence was of the order of 15%. Our figure for the incidence of rheumatic activity in the over-all group, 45%, is not dissimilar to that of Dr. Glover and Dr. Andrus. No difference in clinical improvement was noted between the two age groups.

Our series of operations for mitral disease now numbers nearly 600. Among the first 100 patients, 17 had embolization, and among the last 100, there were 7 with this complication. Fortunately, embolism did not cause death in all these patients. This reduction in incidence of embolism, I believe, is due to ligation of the vessels to the head during the period embolization is most likely to occur. Dr. Bailey's method is useful and should be extended to include the subclavian artery because of the likelihood of vertebral embolization.

[Slide] I shall attempt to describe a basis for choosing patients for surgical correction of mitral valve disease.

The Group I patient with only the murmur of mitral stenosis should not be subjected to operation, as Dr. Glover pointed out.

Patients of Group II have the murmur of mitral stenosis, but are maintaining a compensated state. Surgery can be considered elective, and it is proper to recommend it for this group. The mortality should be negligible, assuming that the patients have normal sinus rhythm without calcification of the valve or damage to the myocardium, lungs, or liver.

About 400 patients of Group III are in our series. This forms a substantially significant statistical number. The mortality rate is now 2.8%. Death occurred in patients with fibrillation or calcification of the valve. In other words, the deaths were due to embolization. Patients of Group III without fibrillation or calcification presumably have no mortality, or virtually none. This group in our series included even patients under stress of pregnancy. Pregnancy, as you know, is an indication for operation if the patient fails in the first trimester because of mitral stenosis. Through the operation, the stenosis is interrupted rather than the pregnancy.

Our series includes nearly 200 patients of Group IV. The mortality rate for these patients was more than 25%. Death in this group had two causes: progressive congestive failure and static but uncorrectible congestive failure. For patients in the static state, death, for the most part, was caused by embolization and, occasionally, by electrolyte imbalance. Those with progressive congestive failure, in whom in spite of a good medical regimen the liver enlarged and fluid retention increased, had the added problem of adrenal exhaustion. However, the electrolyte imbalance was the more important problem.

It is no fairer to comment on the effects of cardiotomy and valvular blasting for mitral stenosis in hundreds of cases, as is done now in many clinics, than it is to discuss the results of lobectomy in series made up of cases of bronchiectasis, lung abscess, carcinoma, and tuberculosis. Mitral stenosis is a spectrum of disease, and within the spectrum the physician has varied responsibility to the patient. One of these responsibilities is to exclude no one from surgery because he is too ill to withstand the procedure. We are obliged to offer surgery to most patients with limitation due to mitral block.

The physician can distinguish in this entire group of patients those who are only progressively disabled by mitral stenosis and who will have no mortality rate. At the other end of the spectrum are the patients who, through embolization, electrolyte imbalance, and adrenal cortical failure or exhaustion, have a mortality rate of up to 30%. Therefore, the physician's responsibility becomes acute.

DR. CHARLES P. BAILEY, Philadelphia: Our series now approaches 1,100 patients, including those with suturing of the valve because of regurgitation, with simultaneous suppression of

aortic stenosis. I would like to point out, along with Dr. Harken, that protection of the brain is possible by constricting the corroded dead vessels, and perhaps the subclavian artery also, with tourniquets of umbilical tape placed around the vessel in the mediastinum.

Our incidence of cerebral embolization in 235 cases without this protection was 5.5%. In 400 subsequent cases with protection, the incidence was less than 1%.

As Dr. Harken pointed out, it is valuable to classify the cases into four groups according to the American Heart Association's criteria. However, it is difficult to obtain comparable classifications in different series because of the personality factors. For instance, after operation, most of a series of 40 patients considered to be in Group I reported that they were able to do more than they could prior to surgery. Many persons would have considered them to be in Group II.

Even we are divided on whether the pleuropericardial reactions mentioned are actually of rheumatic origin or are caused by trauma and the presence of blood in the pericardium. In nonrheumatic patients it seems to me that these reactions are probably related to blood in the pericardium and the necessary trauma of surgery.

Recently, in a small series of cases, I followed the principle of leaving the pericardium widely open when the hope that the complete evacuation of the pericardial contents will lessen the possibility of subsequent febrile reaction.

Dr. E. Cowles Andrus, Baltimore: If I understood Dr. Harken correctly, he mentioned that patients with normal sinus rhythm, even though the valves were calcified, were less likely to have emboli. If that is true, we have been most unfortunate in that serious complications occurred in two of our patients with normal sinus rhythm and calcified valves.

This study was supported in part by a grant from the Heart Association of Maryland.

HYPOTENSIVE ANESTHESIA FOR RADICAL PELVIC AND ABDOMINAL SURGERY

C. PAUL BOYAN, M.D.
NEW YORK

HYPOTENSIVE anesthesia to reduce bleeding during surgery has recently evoked a great interest among surgeons and anesthesiologists. For the past two years we have been using hypotensive anesthesia in selected cases of radical pelvic and abdominal surgery at the Memorial Cancer Center in New York City. The physiological basis for this type of anesthesia will be discussed very briefly.

It is known that the blood pressure varies mainly as the product of cardiac output and peripheral resistance; blood pressure equals cardiac output times peripheral resistance.

In case of hemorrhage the blood volume is reduced, leading to decrease in venous return to the heart, with subsequent fall in cardiac output. The compensatory mechanism of the body acting via the sympathoadrenal system tries to maintain normal blood pressure levels by increasing the peripheral resistance. The produced vasoconstriction achieves temporarily this goal, but with further blood loss the blood pressure falls and reaches low levels. This type of hypotension is called hemorrhagic hypotension. If the other component, i. e., the peripheral resistance, is lowered, the blood pressure will fall, but there will be no reduction in blood volume. The main part of the peripherovascular resistance is encountered in the arteriolar bed of the circulatory system, and there is the place where the biggest drop in the arterial blood pressure occurs, as shown in Chart 1.

The arterioles are kept in tone by impulses conveyed by the sympathetic nervous system. If the latter is blocked by a high spinal anesthesia or a ganglionic blocking agent, the arterioles will dilate; the peripheral resistance will decrease, and as a consequence the blood pressure will fall. This is an example of neurogenic hypotension. Theoretically, if the systolic blood pressure remains above 32 mm. Hg, which is the normal reading at the arteriolar end of the capillary bed, the tissue metabolism will not suffer, because such pressure will be sufficient to maintain normal capillary circulation (Chart 1). It has been observed that normal persons with a blocked autonomous nervous system did not display a great fall in blood pressure while lying supine, but, when they assumed other positions, permitting pooling of blood in the dependent parts of the body, the blood pressure showed a greater drop. The explanation is that the gravity in absent or reduced peripheral resistance begins to play an

From the Department of Anesthesiology Memorial Center for Cancer and Allied Diseases.

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important role in the venous return to the heart. Therefore, proper positioning of the patient on the table according to the principle of postural ischemia is a part of the hypotensive anesthesia technique.

The outstanding features of the two types of hypotension just discussed are represented in Table 1. The main difference is in the blood volume (normal or reduced) and the status of the peripheral vascular resistance (vasoconstriction or vasodilatation).

The postulates we think are essential for this type of anesthesia are the following:

1. Lowered peripheral vascular resistance (arteriolar dilatation) can be produced, as mentioned above, by high spinal block or ganglionic blockade. The main ganglionic blocking agent is hexamethonium bromide. It compares with the acetylcholine released at the ganglionic synapses, producing a temporary blockade.

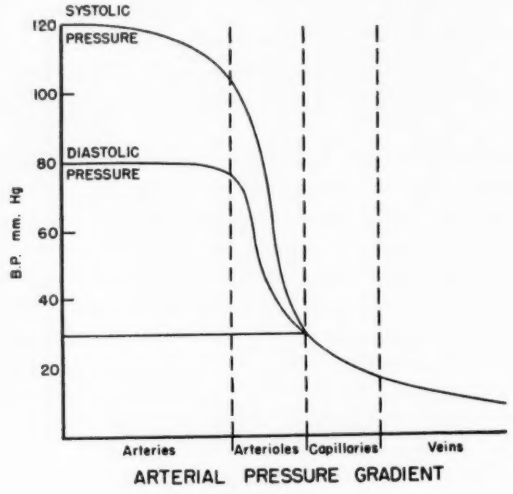

Chart 1.

2. Any deficit in blood volume should be detected preoperatively and corrected by blood replacement. This must be done, because patients with reduced blood volume, being in chronic shock, do not do well during surgical procedures. In addition to this, all blood loss has to be replaced quantitatively as soon as possible.

3. Adequately oxygenated blood is a conditio sine qua non, and a patent airway should be maintained at all times.

4. The head-down position of the patient has been included for the following reasons: When the peripheral resistance has been reduced or abolished, the gravity permits a certain amount of blood pooling in the dependent parts of the body, and therefore the head should be in a position where gravity will help the blood circulation. We have seen, in patients subjected to hypotension and placed in reverse Trendelenburg position, the jugular veins practically emptied of blood, and unanesthetized patients under the same conditions have fainted in our arms, which is not

a sign of efficient blood circulation in the brain. A compromise with this postulate can be accepted in neurosurgical procedures, and the patient can be placed in reverse Trendelenburg position, although this step should be taken as a calculated risk.

The hypotensive anesthesia technique is as follows:

After proper premedication the patient is given intravenous thiopental (Pentothal) sodium, supplemented by tubocurarine chloride, and a plastic endotracheal tube of adequate bore is introduced orally. Then the patient is attached to an ether-oxygen absorption circle and placed in proper position. For pelvic surgery a head-down tilt of about 30 degrees, with knees acutely bent, is sufficient, and, although the operative field is not the highest point, the postural ischemia produced in this way has proved to be satisfactory for all clinical purposes. Supine jack-knife position is assumed when upper abdominal surgery is to be performed, i. e., liver, pancreas, etc. Here the head-down principle has been preserved, and a maximal postural drainage of blood from the operative field has been achieved. A semilateral jackknife position is recommended for thoracoabdominal approaches.

After positioning of the patient, the blood pressure is reduced by intravenous administration of hexamethonium bromide in doses ranging from 10 to 100 mg.

TABLE 1.—*Hypotension*

	Hemorrhagic	Neurogenic
Blood volume	Reduced	Normal
Peripheral resistance	Increased	Reduced
Skin	Pale, cyanotic, clammy, cold	Pink, warm, dry
Pulse	Tachycardia (+++)	Normal; tachycardia (+)
Venous pressure	Reduced (+++)	Normal or reduced (+)

Blood pressure falls to 65 to 70 mm. Hg systolic in most instances and is maintained at that level with additional doses, if necessary. It is desirable to have the hypotensive state for not longer than 60 to 90 minutes. After the excisional surgery has been completed, the blood pressure is brought back to about 100 mm. Hg by elevating the legs, changing the patient's position to almost horizontal, and by a slow infusion of phenylephrine (Neo-Synephrine) hydrochloride or another vasopressor agent of a dilute solution. After thorough hemostasis has been secured with the elevated blood pressure, the abdomen is closed. During the immediate postoperative period the patient has to be watched closely in order to differentiate any subsequent hypotension caused by hemorrhage from a prolonged action of hexamethonium bromide.

Charts 2, 3, 4, and 5 represent the anesthesia records of patients who were subjected to radical surgery under hypotensive anesthesia.

The various types of operations performed during the two-year period are summarized in Table 2. Most of these procedures were of radical nature and usually require considerable blood replacement. The degree of ischemia at the operative field in the aforementioned surgical procedures achieved by this type of hypotensive anesthesia is presented in Table 3. Most of the unsatisfactory results were with young adults and, although many received large amounts of hexamethonium bromide, the blood pressure could not be lowered to a satisfactory level. The best results were obtained with the 45 to 60 years of age group.

This report is based on a series of 114 patients, 16 men and 98 women. Their ages varied between 13 and 64 years, but most were in their fifth or sixth decade.

All patients were selected for clinically unimpaired cardiovascular, renal, and respiratory functions. The anesthesia was satisfactory in all instances. The recovery time was not prolonged, and the incidence of vomiting seemed reduced. The impression of the surgical team is that not only the blood loss was reduced but also concomitantly the tissues were more exactly dissected; principle blood vessels were more

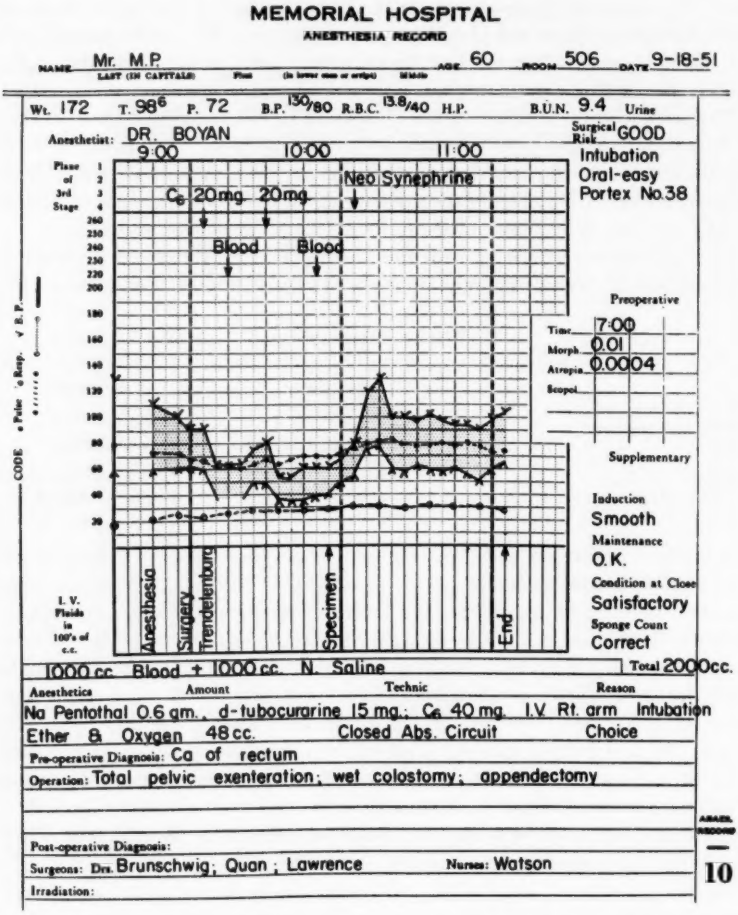

Chart 2.—Anesthesia record of Mr. M. P. Operation consisted of total pelvic exenteration, wet colostomy, and appendectomy for cancer of the rectum. The blood pressure was maintained at 60 to 65 mm. Hg systolic by two 20-mg. doses of hexamethonium bromides. Infusion of dilute phenylephrine hydrochloride solution brought the blood pressure to 100 mm. Hg systolic before the abdomen was closed. The operation lasted 120 minutes, and 1,000 cc. of blood was infused to replace the loss.

easily and cleanly visualized for isolation and dissection, and, insofar as cancer surgery is concerned, areolar tissues and lymph nodes were dissected in block in a more satisfying manner than is the case under ordinary anesthesia at usual blood

pressure levels. In most instances the blood pressure was maintained at 55 to 70 mm. Hg systolic, and only nine patients were subjected to hypotension longer than 80 minutes. The longest period of hypotension was 200 minutes of 60 to 70 mm. Hg. In five patients the blood pressure could not be recorded for a period of 5 to 35 minutes, although the carotid pulse was palpable at all times. The pulse rate did not

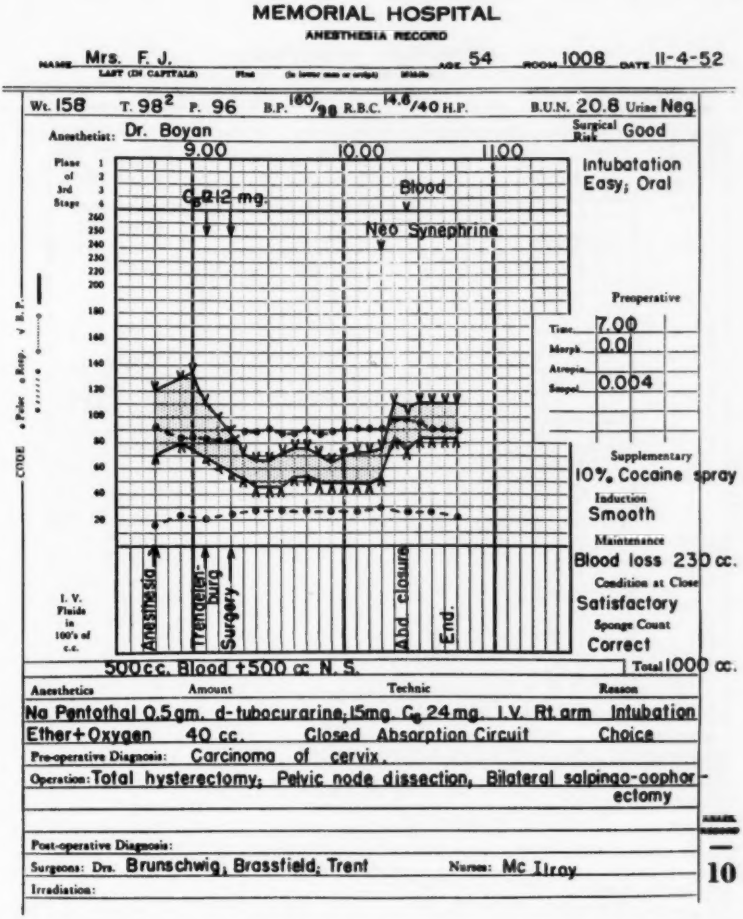

Chart 3.—Anesthesia record of Mrs. F. J. Operation consisted of total hysterectomy, with pelvic node dissection for cancer of the cervix. Blood pressure was maintained at 65 to 75 mm. Hg systolic. Pulse and respiration remained steady. The operation lasted 90 minutes, and the blood loss was 230 cc.

show significant change and remained the same during the hypotensive state. In a few instances it has increased to 120 beats per minute, being regular and maintaining good quality. Electrocardiogram studies were done on 20 patients before and after hypotensive anesthesia; these were comparable to the findings in patients submitted to similar operative procedures in a normotensive state. The urinary output and

blood urea nitrogen were recorded in most of the cases for the first postoperative days; there was no deviation from the records of control patients. Postoperative hemorrhage of significance was encountered in two patients who received 4 and 6 pints (2,000 and 3,000 cc.) of whole blood, respectively, during the immediate postoperative period. Few required 1 or 2 pints (500 or 1,000 cc.) of blood to cover the blood accumulated in the abdominal packs. Ten patients had minimal pulmonary

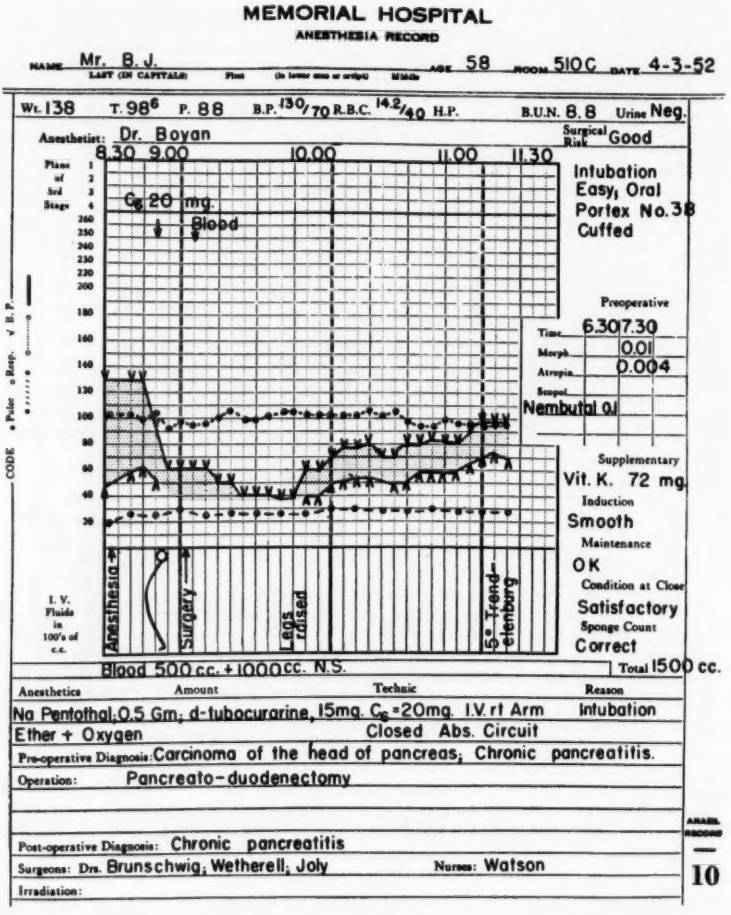

Chart 4.—Anesthesia record of B. J. Operation was pancreatoduodenectomy. Twenty milligrams of hexamethonium bromide lowered the blood pressure to 40 to 60 mm. Hg systolic. No vasopressor was administered, because the blood pressure rose to 90 mm. Hg by changing the position from supine jack-knife to slight Trendelenburg. The operation lasted 130 minutes, and 500 cc. of blood was given to replace the loss.

atelectasis, and another had pneumonia, with transient cardiac irregularities. Thrombophlebitis developed in one of the legs in seven patients. The blood pressure could be easily stabilized postoperatively by keeping the legs elevated or by administration of phenylephrine hydrochloride by intravenous drip when the first measure was not

sufficient. In three patients the blood pressure was unstable postoperatively, necessitating intermittent administration of phenylephrine hydrochloride during a period of a few hours. The mental status of all patients was carefully checked, and there were no detectable changes postoperatively. There were two deaths which we think were due to the anesthesia. One patient died on the third day after prolonged and gen-

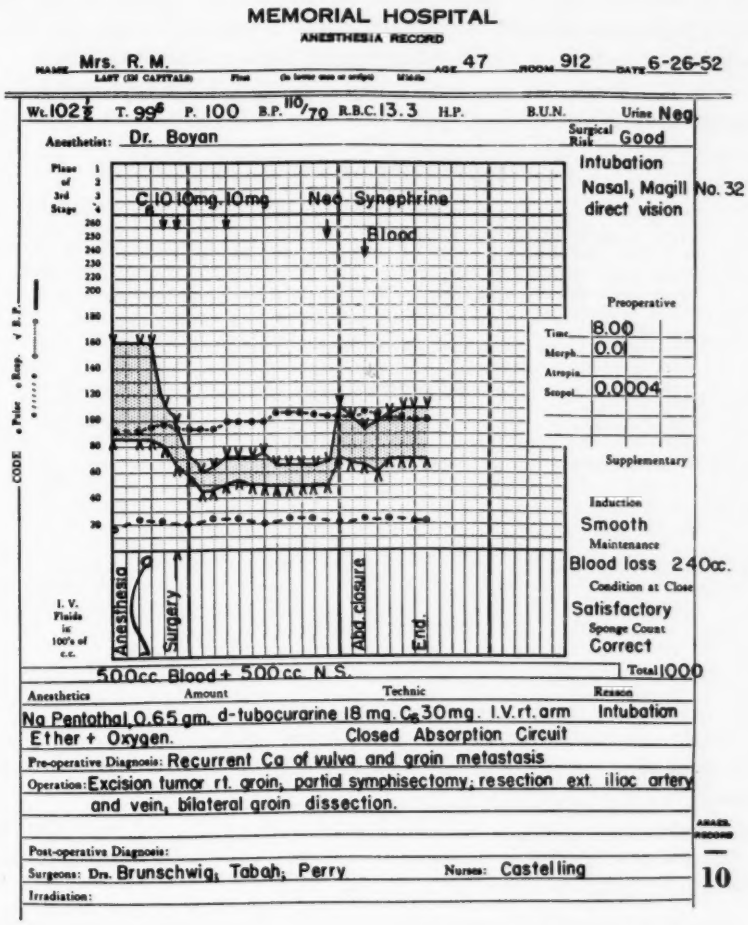

Chart 5.—Anesthesia record of Mrs. R. M. Operation consisted of excision of tumor of the right groin, partial symphysectomy, resection of the external iliac artery and vein, and bilateral groin dissection. Note the precipitous fall in systolic blood pressure to 60 to 70 mm. Hg which lasted 60 minutes and was produced by 30 mg. of hexamethonium bromide, given in divided doses. Blood loss was 240 cc.

eralized bleeding in the operative site, and the other died three hours postoperatively after perfect recovery from anesthesia, with signs of sudden cardiovascular collapse, which did not respond to immediate intensive treatment. Strangely enough, these two patients were subjected to hemipelvectomy.

There are several problems raised in connection with the induced hypotension during anesthesia which require further investigation before this type of anesthesia can be accepted as a standard technique. The oxygenation of the brain is of prime importance. All clinical signs indicated that there was no impairment, in that the patients remained pink in color and the capillary refilling time on the forehead was brisk. It was noted that the abdominal viscera, which in the Trendelenburg position are of a level higher than the brain, showed good oxygenation. This also strongly suggested that the brain in its dependent position did not suffer from anoxia.

There is evidence that the cardiac output during induced hypotensive state is reduced, but its extent and significance has yet to be determined. There is a sound

TABLE 2.—*Type of Operations Performed*

Radical hysterectomy and node dissection	33
Total pelvic exenteration	16
Partial pelvic exenteration	10
Pancreaticoduodenectomy	4
Partial hepatectomy	6
Hemipelvectomy	6
Resection of pelvic or abdominal tumors	11
Major orthopedic operations	6
Total vulvectomy and groin node dissection	8
Bilateral adrenalectomy	1
Radical mastectomy	6
Thoracoabdominal gastroesophagectomy	1
Exploratory laparotomy, liver biopsy, etc.	11
Total	114

TABLE 3.—*Degree of Ischemia in the Operative Field*

Excellent	65
Good	33
None observed	16
Total	114

basis to the speculation that, in spite of diminished coronary blood flow due to low blood pressure, the myocardium does not suffer, because the absence of peripheral resistance has diminished its work greatly. The oxygen need has been reduced more than the decrease in supply, thus leaving the myocardium with relatively better oxygenation than during a normotensive state. As previously stated, these are theoretical explanations supported by clinical results only.

That there was no oliguria or anuria of significance in the immediate postoperative period of the patients in this series shows an unimpaired cell metabolism in the kidney during the hypotensive state, although the urine filtration should diminish with lowering of the blood pressure and cease when it reaches below 75 mm. Hg systolic. Experimental work carried out at the Memorial Hospital confirms this assumption.

The hypotension should be maintained as long as it is necessary to remove the specimen and secure hemostasis. At the present time our desire is not to exceed 75 to 100 minutes, with low systolic pressure of about 65 to 70 mm. Hg.

During this type of anesthesia the anesthesiologist must be constantly on the alert to observe for proper oxygenation and changes in blood pressure and pulse and to correct blood loss.

Hypotensive anesthesia is still under investigation, and impaired cardiovascular, renal, and respiratory functions represent, so far, a definite contraindication for this technique.

It is our distinct impression that hypotensive anesthesia has a place in selected cases in radical surgical procedures for advanced cancer.

ABSTRACT OF DISCUSSION

DR. ALEXANDER BRUNSCHWIG, New York: Dr. Boyan has reviewed in detail our experiences with hypotensive anesthesia, a method introduced to reduce the possibility of excessive hemorrhage in connection with ultraradical resections for cancer. One cannot undertake massive resections for advanced cancer without encountering hemorrhage and, therefore, without subjecting the patient to the dangers of shock. It is understandable that surgeons have been hesitant to accept the idea of willful induction of a hypotensive state in which the systolic blood pressure is at low levels that ordinarily denote profound surgical shock. That this is feasible and that this hypotensive method has certain advantages has been demonstrated in Dr. Boyan's report. About 10 years ago the late Dr. Dallas B. Phemister published a series of experiments in rabbits in which he showed that generalized vasodilatation resulting from stimulation of a cardiodepressor nerve resulted in a marked hypotension, i. e., a systolic blood pressure of between 20 and 40 mm. of mercury. This hypotensive state could be maintained for eight to nine hours before the animal died. Control experiments showed that when comparable low levels of systolic blood pressure were obtained by bleeding the animals, this type of hypotension was dangerous, and none of the animals survived beyond four hours. Phemister also showed that in a hypotensive state in rabbits with generalized vasodilatation there was dilution of blood because of the inflow of fluids from the tissue spaces. This is understandable, because with generalized arterodilatation extra space is created which must be filled by fluids from somewhere. In three patients, Dr. Kate Roberts of the Sloane Kettering Institute confirmed the experimental observations; she showed that there was hemodilution when hypotension was maintained in these patients for a period up to an hour. Obviously, it is not possible to test the length of time that a human being will survive a hypotensive state, but we are sure that for periods up to an hour or an hour and a half an induced systolic blood pressure of 60 or 70 mm. of mercury, resulting from sympathetic ganglion paralysis by hexamethonium, is not dangerous. We have had one instance in our series where the hypotensive state was maintained for a little over three hours with survival of the patient and no untoward sequelae. As in many clinical investigations, especially in the operating room, control observations are very difficult to secure, if not impossible. We know that in some extensive operations the combination of various circumstances renders such operations almost bloodless, and yet at the outset severe hemorrhage may be anticipated. With some exceptions, however, it is my very distinct impression that the induced hypotensive state with hexamethonium contributes to a reduction in the amount of hemorrhage that occurs in operations where large raw surfaces are created. We have some data in support of this view, but again these are not rigidly controlled observations. For example, in nine total pelvic extenterations under normotensive anesthesia, the average blood transfused was 4,000 cc. per patient. In 12 patients who received hypotensive anesthesia, the blood transfused was a little over half this amount per patient. In 8 radical hysterectomies and pelvic node excisions the average blood transfused was 3,000 cc. per patient. In this operation we take great care to strip out the fatty areolar tissues and nodes from the deep lateral portions of the pelvis, especially around the sciatic nerves. This is where oozing of blood and entrance into large veins is apt to occur. In 21 similar operations with hypotensive anesthesia this amount of blood transfused was slightly over half the amount per patient.

Once the operation performed under hypotensive anesthesia is terminated and all vessels have been secured and ligated, the pressure is brought up before the abdomen is closed in order that unligated vessels that are capable of bleeding when the pressure is elevated can be clamped and ligated. Hypotensive anesthesia is not indicated as a routine method. It is to be employed

only in unusual instances and, of course, especially where loss of blood in excessive quantities may be anticipated. Furthermore, it is a method that must be employed by a physician-anesthetist well versed in pharmacology and in the physiology of the anesthetized patient. Disastrous results will certainly follow its employment by those who are not very familiar with all phases of anesthesiology, and therefore the use of hypotensive anesthesia will be limited. But where there is a clear-cut indication for it and where the proper personnel is available for its conduct, I believe that it is a valuable adjunct to the supportive treatment of surgical patients. I use the word "supportive," because it is a measure employed to prevent shock from hemorrhage.

DR. CHARLES L. BURSTEIN, New York: I wish to congratulate Dr. Boyan and Dr. Brunschwig for their pioneering work on hypotensive anesthesia during surgery. I am in full agreement with the benefits of this technique. I should like to reemphasize that the hypotension produced is of a particular kind, namely, by blocking the automatic ganglia. This results in peripheral vasodilatation, so that the terminal tissues and terminal cells are nourished adequately, even though the pressure in the large arteries is reduced. Actually, it is the circulation to and from the terminal tissues that is important. Paton, of London, and Moyer, of St. Louis, have reviewed the pharmacology of the methonium compounds recently and have shown that the vital organs (brain, heart, and kidneys) are not affected by these drugs, even when the pressure in the large arteries is reduced to 70 or 60 mm. Hg.

At the Hospital for Special Surgery, where we have had the opportunity to use this technique in spine fusions and open hip operations, it was observed by means of direct-writing electrocardiography that the electrocardiogram remains normal after the administration of hexamethonium bromide, even when the brachial arterial blood pressure is barely perceptible. Our technique has been to administer a dose of hexamethonium bromide to produce a desired level of hypotension. This usually lasts one to two hours, at which time the surgical procedure is completed. We do not like to give any vasoconstrictor drug to raise the blood pressure, because this would produce peripheral vasoconstriction with deficient peripheral circulation, a condition that should be avoided.

Work is in progress on the use of more promising ganglion-blocking drugs which are brief in duration. Administration of such drugs by intravenous drip can maintain a desired level of hypotension, and, when no longer required, cessation of administration results in return to normal blood pressure level without the superimposed production of peripheral vasoconstriction.

As a final remark, it should be borne in mind that hypotension in large vessels and peripheral vasodilatation are not the only beneficial results obtained by automatic ganglion-blocking agents; another worthwhile consideration is the reduction in autonomic circulatory reflexes that is obtained by this same mechanism of blocking the autonomic ganglia (for example, vagal reflexes, carotid sinus reflexes, or celiac plexus reflexes).

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FRACTURES OF THE ANKLE

V. Pronation-Dorsiflexion Fracture

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IN REVIEWING the literature it is found that authors writing on clinical, experimental, and roentgenographic aspects found fractures which according to the operative findings (Lauenstein, Volkmann) and roentgenographic appearance (Meissner, Svend Hansen) had a fragment torn from the tibia anterolaterally or a large fragment torn off from the anterior lip of the tibia. By a closer study of the literature, it will be noticed that in reports on fractures with a large fragment torn from the anterior tibial lip, illustrated by roentgenograms in two planes,[1] fracture in the base of the medial malleolus is invariably found[2] (Fig. 1).

A review of the case records of these fractures demonstrates that the fractures are always produced by a fall on the foot from a considerable height (10 to 13 ft. [3 to 5m.], three or four stories).

According to the mechanism of fall, the foot will go into pronation by the pressure exerted against the planta and will become vigorously dorsiflexed, and the trochlea tali will be forced up into the malleolar fork (tibiofibular mortise).

The trochlea, which, as previously pointed out, has the form of a truncated cone, will act as a wedge on the "cup-like" malleolar fork and produce a fracture in the base of the medial malleolus.[3]

If a fracture in the medial malleolus has occurred, the dorsiflexion of the talus may be increased. In addition, the talus is luxated a little forward because after fracture of the medial malleolus the deltoid ligament does not retain it. Since only forward subluxation of the talus is possible, the superior surface of this bone will remain in contact with a very considerable (anterior) part of the distal articular surface of the tiba. A large fragment, always of a uniform and characteristic form, will be torn off from the anterior part of the tibia if the traumatic dorsiflexion of the foot is powerful enough to produce such a massive fragment. To do this a great exertion of force is required, which is in keeping with the observation that the fracture is always produced by a fall from a considerable height.

From the Central Hospital.

1. Dieterle, J.: The Use of Kirschner Wire in Maintaining Reduction of Fracture Dislocation of the Ankle Joint, J. Bone & Joint Surg. **17**:990, 1935. Lauge-Hansen, N.: Ankelbrud, Thesis, Copenhagen, 1942. Potherat: Fracture verticale de l'extremité inférieur du tibia, Bull. et mem. Soc. chir. Paris **35**:1296, 1911. Schneck, F.: Röntgendiagnostik der Knochenverletzungen, Vienna, Wilhelm Maudrick, 1932. Tanton, J.: Fractures du membre inférieur, in Nouveau traité de chirurgie, Paris, Le Dentu et Delbet, 1916, Vol. 4, pp. 120-232.

2. Lauge-Hansen, N.: Fractures of the Ankle: I. Analytic Historic Survey as the Basis of New Experimental, Roentgenologic, and Clinical Investigations, Arch. Surg. **56**:259, 1948.

3. Lauge-Hansen, N.: Fractures of the Ankle: II. Combined Experimental-Surgical and Experimental-Roentgenologic Investigations, Arch. Surg. **60**:957, 1950.

In agreement with the fact that the fracture has been produced by forced dorsiflexion, the fragment will invariably be displaced proximally and anteriorly.

The analysis of the pathoanatomical findings at autopsy and dissection of the fractured region in a case reported below establishes the conformity of this with the assumed mechanism of fracture (Fig. 2).

A careful dissection of the fractured ankle-joint region was performed on the 12th day following the fracture.

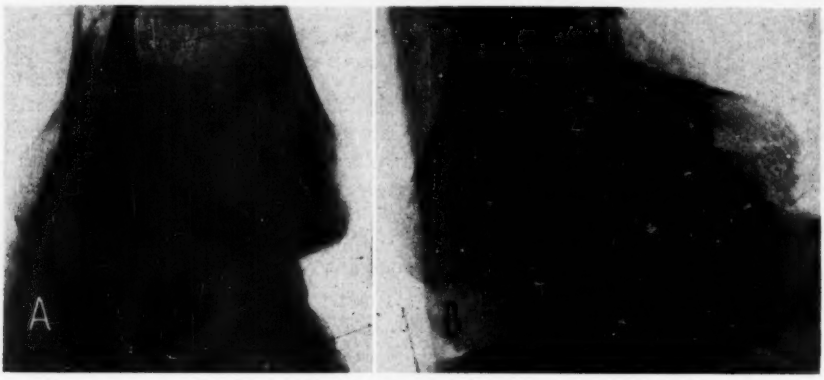

Fig. 1.—Pronation-dorsiflexion fractures: fracture in the base of the medial malleolus with a large fragment torn from the anterior lip of the tibia. Note displacement of the fragment and anterior subluxation of the talus.

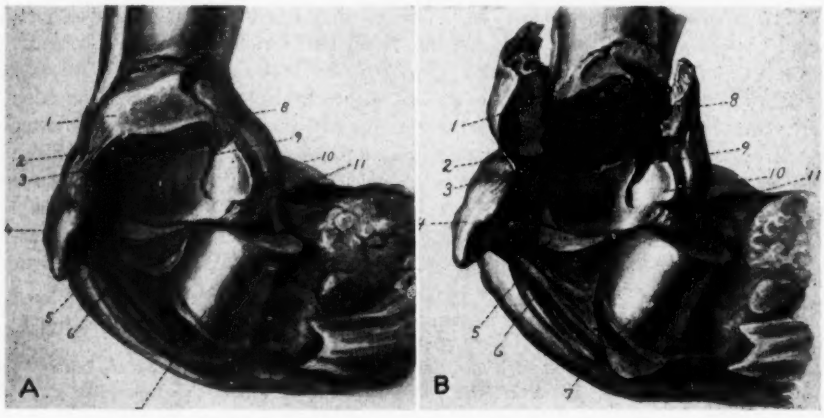

Fig. 2.—Pronation-dorsiflexion fracture (large fragment torn from the anterior lip of the tibia in association with fracture in the base of the medial malleolus). *A*, drawing of autopsy specimen: large fragment of the anterior lip of the tibia with the anterior third of the distal tibial articular surface (1); ligamentum malleoli lateralis anterius, intact (2); fractural diastasis of 5 or 6 mm. on the tibial articular surface (3); lateral malleolus (4); ligamentum malleoli lateralis posterius distale (5); ligamentum talofibulare posterius—note insertion on talus (6); talus (7); intermediate fragment at the anterior corner of the medial malleolus (8); fractural space in the medial malleolar fracture, which does not reach the posterior margin of the distal tibial articular surface (9); medial malleolus (10); interosseous part of the deltoid ligament (11). *B*, broken surface on the tibia, forming a slightly convex curve anteriorly (3).

After the skin and subcutaneous tissue was removed, a tear, the size of a bean, was demonstrated in the posterior wall of the articular capsule of the ankle joint, but otherwise no signs of lesion of the capsule, ligaments, tendons, or tendon sheaths around the ankle joint were found.

The periosteum of the tibia was also intact, but through it a fracture in the base of the medial malleolus was palpable, and the fracture line here ran in a curve proximally on the medial surface of the tibia from the anterior to the dorsal corner of the medial malleolus. A fracture was also felt distally on the anterior surface of the tibia. The fracture line ran in a curve on the anterior surface of the tibia from the anterior corner of the medial malleolus proximally to 3.5 cm. above the space of the ankle joint and continued to the anterolateral corner of the tibia medially to the tibial insertion of the ligamentum malleoli lateralis anterius.

The foot could be dorsiflexed to an abnormally great extent. The fragments moved only a little on movements of the foot. In particular, it was not possible to change the position of the fragment by forced plantar flexion of the pronated or supinated foot.

The anterior part of the medial malleolar fragment protruded some millimeters medially and the fragment from the anterior lip of the tibia, some millimeters frontally.

When the talocrural joint (frontally and laterally) was opened, it was found to be filled with blood. No signs of ligamentous lesions were seen by inspection from the joint cavity.

In the articular surface of the tibia there was a fracture running anteroposteriorly on the border between the articular surface of the medial malleolus and the distal articular surface of the tibia (Fig. 2*A*).

The fracture did not quite reach the dorsal margin of the articular surface of the tibia. The fractural space in the articular surface was widest anteriorly, where it measured approximately 2 mm. The direction of the fracture through the base of the medial malleolus was vertical rather than horizontal.

Furthermore, there was a transverse fracture through the whole of the distal articular surface of the tibia parallel with its anterior margin and 1 cm. dorsal to it. The fractural space in the articular cartilage was 0.5 cm.

The fragments were impacted, and it was impossible to reduce them, even by direct pressure.

The fragment was rather flake-like and consisted mainly of the articular surface and the cortical part of the tibia; the broken surface facing backward was slightly concave. The broken surface of the tibia was correspondingly convex (Fig. 2*B*).

An intermediate fragment, the size of a bean, was found anteriorly between the malleolar fragment and that of the anterior lip of the tibia.

These autopsy findings seem to lend support to the assumption that the fracture in the medial malleolus must be the primary lesion. That the fractural space with direction frontodorsally was widest anteriorly and that the fracture line did not come right through to the posterior margin of the tibial articular surface is in conformity with what has previously been stated, viz., that the anterior part of the articular surface of the medial malleolus is affected rather vigorously in medial and proximal direction by the wedge action of the talus on the malleolar fork when pressure is exerted against the planta and when the foot is dorsiflexed.

Because ankle fractures in which a large fragment is torn off from the anterior lip of the tibia are always associated with a fracture in the medial malleolus and, moreover, because the form and displacement of the large tibial fragment as well as the localization of the transverse fracture line through the distal articular surface of the tibia indicate that this fragment is produced by forced dorsiflexion of the

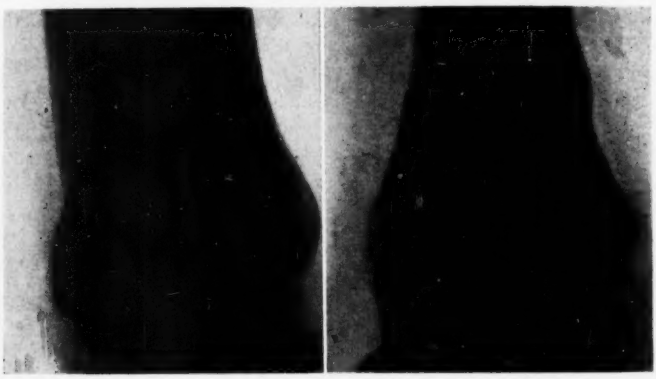

Fig. 3.—Pronation-dorsiflexion fracture. Left, no displacement. Right, osseous union with good bony relationship. No weight-bearing was allowed for 14 weeks.

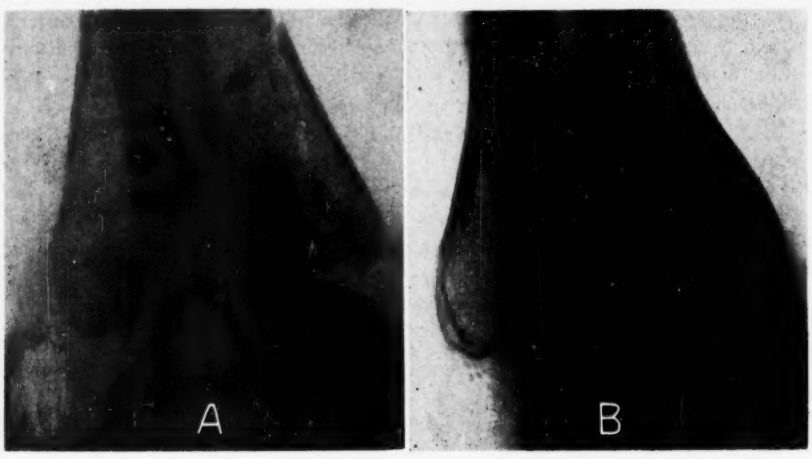

Fig. 4.—Pronation-dorsiflexion fracture: *A*, no displacement; *B*, osseous union with slight displacement and anterior subluxation because patient began weight-bearing in a plaster cast after nine weeks.

pronated foot, this lesion must be considered a special form of ankle fracture [4]; in view of the supposed mechanism of fracture (the foot turned into pronation at the moment when forced dorsiflexion produces the fracture) it seems reasonable, from a genetic point of view, to describe it as a pronation-dorsiflexion fracture.

4. Lauge-Hansen, N.: Fractures of the Ankle: IV. Clinical Use of Genetic Roentgen Diagnosis and Genetic Reduction, A. M. A. Arch. Surg. **64**:488, 1952.

The pronation-dorsiflexion fracture may occur in four stages. The fracture in the medial malleolus represents Stage 1; the avulsion of a large fragment from the anterior lip of the tibia, Stage 2 (Figs. 1, 3, and 4); fracture of the supramalleolar part of the fibula, Stage 3 (Figs. 5, 6, and 7), and the transverse fracture in the dorsal part of the tibia, level with the proximal margin of the large tibial fragment, Stage 4 (Fig. 8). Thus, if Stage 4 is reached, the fracture involves both bones of the leg, with a comminuted intra-articular fracture of the distal end of the tibia.

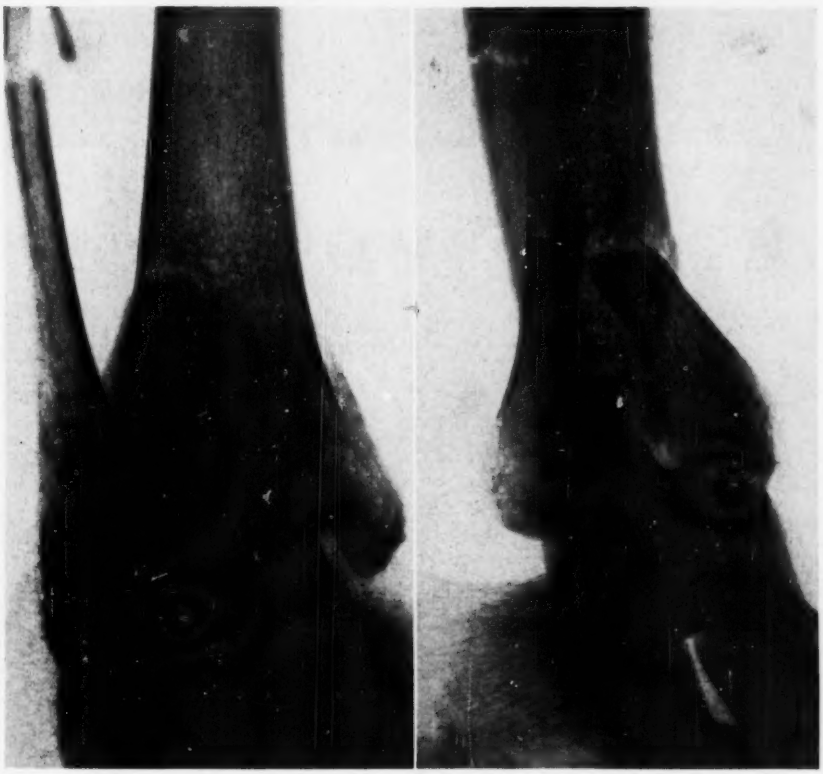

Fig. 5.—Pronation-dorsiflexion fracture, Stage 3. Fracture in the base of the medial malleolus, avulsion of a large fragment from the anterior lip of the tibia and fracture of the supramalleolar part of the fibula. Note the typical displacement and subluxation.

In the presence of displacement in Stages 2 and 3, the large tibial fragment is displaced anteriorly and proximally and at the same time rotated, and the talus is subluxated forward and proximally (Fig. 1 and 5). The same displacement occurs in Stage 4 but is here coupled with lateral displacement, rotation, and angulation, as may be seen in an ordinary fracture involving both bones of the leg (Fig. 8*A*).

It is very difficult to obtain a good anatomical relation and a good functional result in the treatment of pronation-dorsiflexion fracture. An exact knowledge of

the genesis and the pathoanatomical conditions of the fracture is imperative, and it is also important to bear in mind the normal anatomy of the ankle joint, notably the fact that the large fragment from the anterior lip of the tibia is connected with

Fig. 6.—Same fracture as in Figure 5 after reduction. Note maximal plantar flexion of the supinated foot.

the bones of the foot only by means of the joint capsule and not by any ligaments, so that there is no possibility of overcoming the displacement or subsequently maintaining the reduction of this fragment by pulling at the ligaments, as in other types of ankle fractures.

Fig. 7.—Same fracture as in Figure 5, shown seven weeks later after change of plaster cast. Foot is now in midposition, and bony relationship is still good.

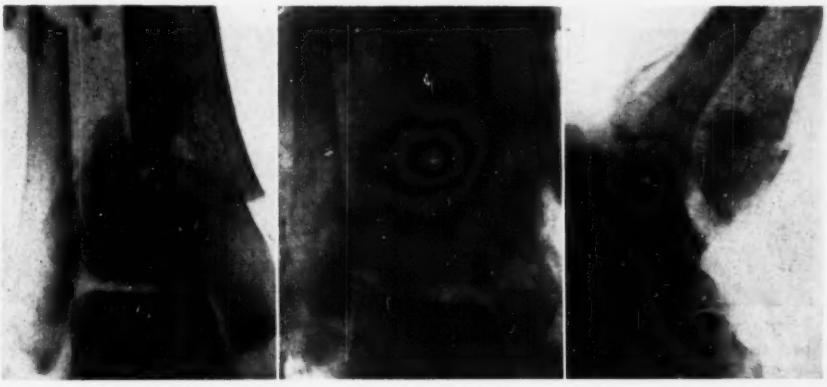

Fig. 8.—Pronation-dorsiflexion fracture, Stage 4. Same lesions as in Stage 3 plus transverse fracture dorsally in the tibia, level with the proximal margin of the anterior tibial fragment. Before and after reduction (right), by which good relationship was achieved.

Fig. 9.—Pronation-dorsiflexion lesion of the epiphysis, Stage 3. Separation of the lower tibial epiphysis with avulsion of a triangular fragment from the tibial diaphysis anteriorly and supramalleolar fracture of the fibula.

Furthermore, it is general experience that the osseous healing of the fragment from the anterior lip of the tibia occurs very slowly, for which reason it is important to avoid any weight-bearing for about 15 weeks. If even slight weight-bearing is allowed before this lapse of time, the talus will slide forward on the somewhat oblique distal articular surface of the tibia, so that the weight is transferred exclusively to the large anterior tibial fragment, which will then become displaced anteriorly if firm osseous union has not been established (Fig. 4).

Reduction of the displaced fragment and the anteriorly subluxated talus in Stages 2 and 3 may be accomplished by direct pressure against the large fragment of the anterior lip of the tibia in distal and dorsal direction with a simultaneous pull at the heel in distal and dorsal direction, while the foot is plantar flexed and supinated. Plantar flexion of the foot tightens the tendons in front of the ankle joint, which exert a pressure against the anterior tibial fragment and thus help to maintain the reduction (Fig. 6). After the reduction the foot should be immobilized in this position by means of a tight-fitting plaster cast. This plantar flexion of the foot should be maintained for four to six weeks, after which time a new tight-fitting plaster cast, with the foot in a position midway between dorsiflexion and plantar

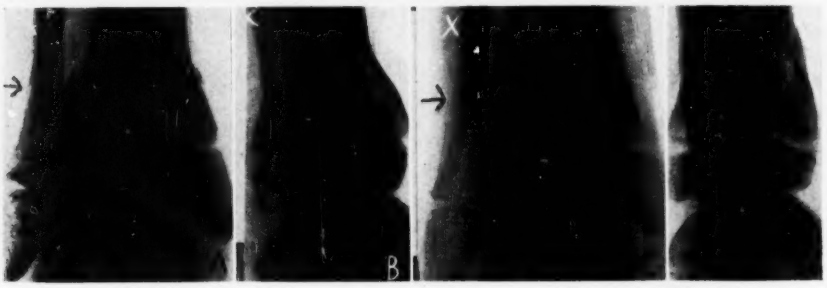

Fig. 10.—Pronation-dorsiflexion lesion of the epiphysis, Stage 4. Same lesions as in Stage 3 plus transverse fracture dorsally in the tibia, level with the upper margin of the anterior tibial fragment. *C* and *D*, four weeks later. Callus shadow indicates the site of the fibular fracture.

flexion, should be applied (Fig. 7). This second cast should be worn for about 10 weeks and no weight-bearing allowed. The position should be checked roentgenographically at frequent intervals to disclose incipient displacement, if any.

In Stage IV reduction, application of plaster cast may be carried out in the same way, but continuous traction by a wire through the calcaneus should also be established to prevent lateral displacement and abnormal angulation.

In children the lesion analogous to pronation-dorsiflexion fracture is separation of the distal tibial epiphysis with a large anterior fragment torn off from the tibial diaphysis. Corresponding to pronation-dorsiflexion fracture, Stages 3 and 4, this epiphyseal separation is associated with fracture of the supramalleolar part of the fibula (Stage 3, Fig. 9) and with a transverse fracture in the dorsal part of the tibia, level with the proximal margin of the large anterior fragment (Stage 4, Fig. 10 *A* and *B*).

Separation of the lower tibial epiphysis does not involve the talocrural joint, all lesions being located extra-articularly. After reduction the ankle joint should be immobilized in a tight-fitting plaster cast for four or five weeks, during which period weight-bearing should not be allowed. After this time has elapsed, good union with distinct callus formation will be in progress (Fig. 10 *C* and *D*).

SQUAMOUS CELL ANAL CARCINOMA

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ANN ARBOR, MICH.

IT IS SAID that surgeons early recognized that epithelioma of the anus was "a peculiarly resistant type of tumor."[1] There is little evidence to show that the epidermoid carcinomas which arise in the anal canal or the perianal skin are different in their intrinsic characteristics from similar lesions occurring elsewhere. Yet, it is true that statistical studies presented up to this time indicate that treatment of this rare neoplasm has not been brilliantly successful. This is most apparent when considering that group of patients with small, locally favorable lesions that are sometimes presented to the surgeon. Good results have not followed uniformly any of the present forms of treatment of the far-advanced, widely disseminated lesion.

CASE 14 (No. 518383).—A 64-year-old housewife had had for four months constipation and anal pain upon sitting down. For these symptoms she had a hemorrhoidectomy. Her pain remained after the operation, and several weeks later an anal ulcer measuring 2 cm. in diameter was widely excised. Histologically this lesion was a slightly cornifying squamous cell carcinoma grade II with infiltration extending into dense connective tissue and smooth muscle. She was seen at the University of Michigan Hospital where two specimens removed from the site of recent excision showed no evidence of carcinoma. Finally the entire area of previous excision was reexcised. Again no residual evidence of neoplasm could be demonstrated. No additional operations were performed.

After leaving the hospital the patient saw her physician at irregular and infrequent intervals. Four years and five months later she developed acute lower bowel obstruction with some bleeding. A biopsy specimen removed from 15 cm. above the anal sphincter revealed squamous cell carcinoma. The cervix and bladder were negative for neoplasm. At this time the patient would not accept an abdominoperineal resection. She died April 29, 1949, six and one-half years after the first histologic diagnosis of squamous cell carcinoma was made.

This patient presented the example of a small, locally favorable lesion but one which originally extended deeply enough to involve muscle. She was also an excellent example of a patient with a four and one-half year "cure" who subsequently died of her neoplasm. It is apparent that mucosal and submucosal residuum of the lesion was not responsible for its recurrence—there is ample evidence of adequate mucosal and submucosal excision. The neoplasm then must have had a greater extension in the deeper intramural bowel layers or lymphatic permeation must have already occurred.

To what extent intramural extension of anal carcinomas differs from that which occurs in the commoner carcinomas of the adjacent rectal segment is unknown. Monsarrat and Williams[2] have suggested from a careful study of four specimens of adenocarcinoma of the rectum that the maximum intramural extension of that

From the Department of Surgery, University Hospital.

1. Raiford, T. S.: Surg., Gynec. & Obst. **57**:21-35, 1933.
2. Monsarrat, K. W., and Williams, I. J.: Brit. J. Surg. **1**:173-182, 1913.

lesion may be no greater than 2½ in. (6.4 cm.) beyond the mucosal extent of the lesion. In one of the patients whom they studied, in whom this maximal extension occurred, the lesion encroached upon the anal canal for one-third of its longitudinal extent. In each of their patients the maximal intramural extension occurred in the adventitia and not in the submucosal or intramuscular lymphatic plexuses.

One need not always look for signs of failure of cure from this disease in the area of local occurrence but rather in the areas of regional and distant dissemination. If the surgeon is to attack this lesion intelligently and vigorously, with the hope of cure, an accurate anatomic foundation must be the primary basis upon which the surgical effort is made. It does not seem amiss then to outline in some detail a few

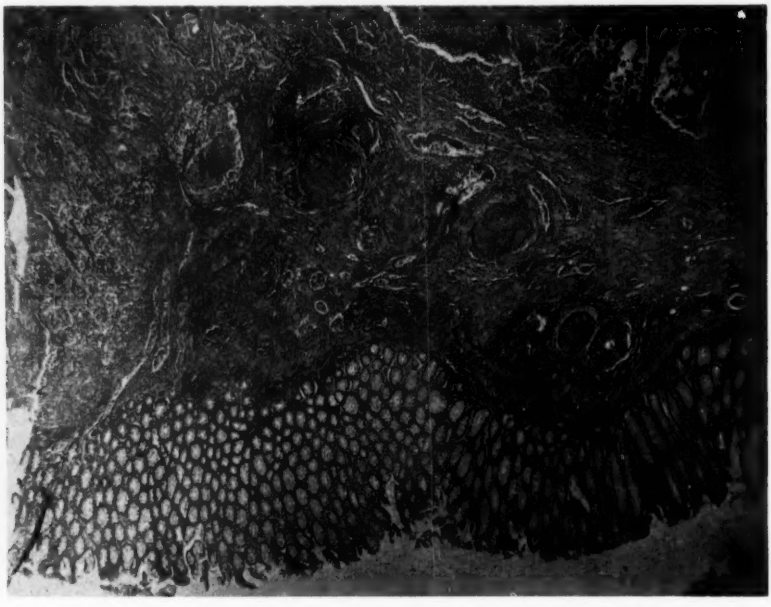

Fig. 1 (Case 6).—Extension of squamous cell carcinoma in rectal wall.

of the basic anatomic characteristics of the anal and perianal area, particularly in their bearing upon the course of dissemination of neoplastic cells from this area.

Too much importance cannot be placed upon the manner in which epidermoid carcinomas extend. Local extension into the sphincter muscles, levator ani muscles and even the perianal tissue is common. Metastases also occur by way of blood and lymph streams; blood-borne metastases are sufficiently uncommon, however, until late in the course of this disease so that their presence is seldom considered in the initial contemplation of treatment of the lesion—unless obvious involvement of other distant structures has already occurred. Rouvière [3] has recorded extensive information upon the lymphatic routes of drainage of the anal canal and perianal skin. Excerpts from this work are quoted in detail in the following paragraphs.

3. Rouvière, H.: Anatomy of Human Lymphatic System, translated by M. J. Tobias, Ann Arbor, Mich., Edwards Brothers, Inc., 1938.

The collecting trunks of the lymphatics of the anorectal area are divided into three groups: (*a*) inferior, (*b*) middle, and (*c*) superior.

(*a*) *The Inferior Collecting Trunks.* These, two to five in number, originate in the cutaneous part of the anus. They run a tortuous course forward and outward in the fatty-cellular subcutaneous tissue of the perineum, the groin, or of the medial surface of the thigh, or even of the pubic region; and empty into the superficial inguinal nodes by terminating in most instances in its superomedial or occasionally in its inferomedial group, or in both of these groups.

All of the lymphatics from the cutaneous anal zone, however, do not run to the superficial inguinal nodes. In eight of Bauley's preparations *a localized injection of the cutaneous anal zone, in three instances extended to the anorectal nodes by collecting vessels which emerged from the rectal wall at the level of the levator ani.*

(*b*) *The middle collecting trunks.* The middle hemorrhoidal and laterosacral lymphatics.

These vessels, one to two in number on each side, emerge from the rectum by three or four rami immediately above the levator ani or at a somewhat higher level. Usually they follow the middle hemorrhoidal vessels but may accompany the lateral sacral or middle sacral arteries, or even . . . the nerves of the pelvic part of the rectum. They may also run alone and apart from the pelvic fascia as observed in one case by Gerota. Poirier and Cunéo describe additional lymph

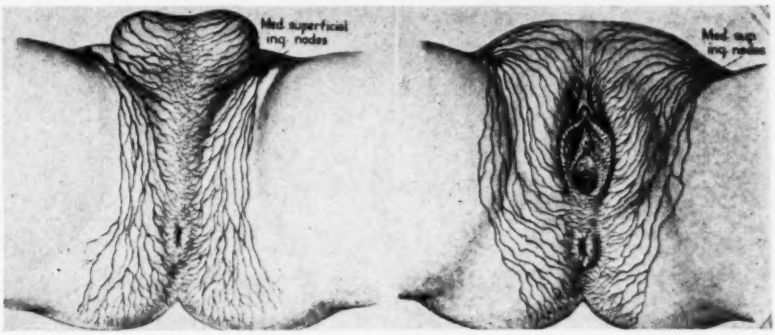

Fig. 2.—Lymphatic communications of the perineum (Pack and Reckers [14]).

trunks which have to be attached to the middle collecting vessels. *These vessels emerge from the wall of the pars analis recti below the insertion of the levator ani* and reach a hypogastric node by following successively the inferior hemorrhoidal and internal pudic arteries (which is rare), or (more often) by perforating the levator ani above the ischiorectal fossa. The lymphatics which accompany the middle hemorrhoidal blood vessels terminate in one of the hypogastric nodes, most often in the node placed at the termination of the hypogastric artery or in a node near the commencement of the middle hemorrhoidal artery. The trunks terminate in these nodes directly or after having traversed a small nodule situated on the course of the middle hemorrhoidal blood vessels (Fig. 3). The collecting trunks which accompany the lateral and middle sacral arteries run to the lateral sacral nodes and to the nodes of the promontory.

(*c*) *The superior* trunks or superior hemorrhoidal trunks.

The regions from which these collecting trunks arise extend throughout the entire length of the rectum, since they drain its entire superior portion. *Some of these trunks descend even as low as the inferior extremity of the anal canal* (Fig. 3). In fact, the middle hemorrhoidal trunks which reach the hypogastric nodes *carry but a portion of the lymph from the anal canal.* In the columns of Morgagni, for example, 'veritable clusters of lymphatics' (Gerota) grouped about the lowest ramifications of the superior hemorrhoidal blood vessels reach the pelvic rectum. *The area of origin for the superior hemorrhoidal trunks extends as low as the anal cutaneous zone.* I have already mentioned that some trunks from this zone ascend towards the rectum and pour their lymph into the anorectal nodes placed along the course of the superior hemorrhoidal blood vessels. The superior trunks which spring from the anal canal, course

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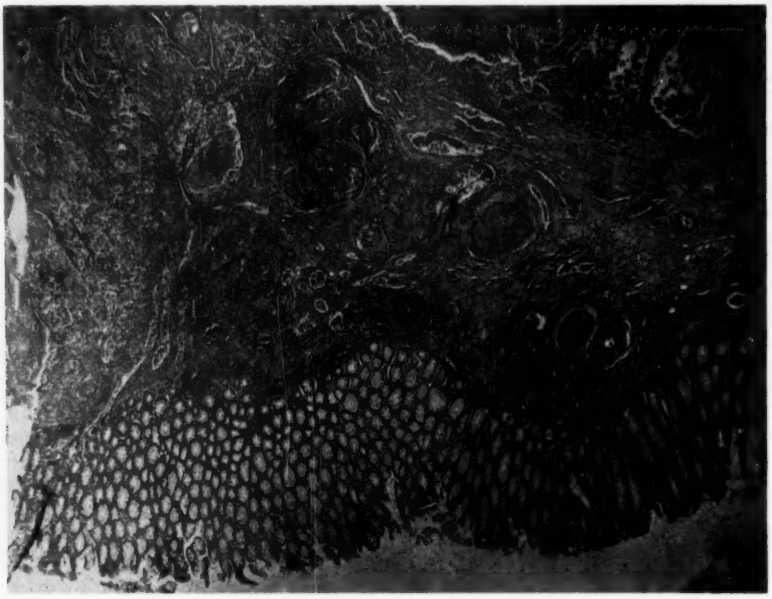

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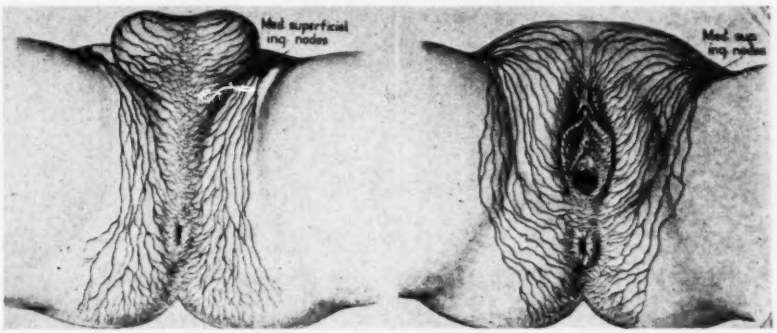

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The regions from which these collecting trunks arise extend throughout the entire length of the rectum, since they drain its entire superior portion. *Some of these trunks descend even as low as the inferior extremity of the anal canal* (Fig. 3). In fact, the middle hemorrhoidal trunks which reach the hypogastric nodes *carry but a portion of the lymph from the anal canal.* In the columns of Morgagni, for example, 'veritable clusters of lymphatics' (Gerota) grouped about the lowest ramifications of the superior hemorrhoidal blood vessels reach the pelvic rectum. *The area of origin for the superior hemorrhoidal trunks extends as low as the anal cutaneous zone.* I have already mentioned that some trunks from this zone ascend towards the rectum and pour their lymph into the anorectal nodes placed along the course of the superior hemorrhoidal blood vessels. The superior trunks which spring from the anal canal, course

between mucous and muscular coats, and, traversing the latter, they emerge from the rectal wall. Whatever the level at which they emerge the superior hemorrhoidal trunks generally follow the rami of the like-named arteries.

The greater number (of these lymphatics) terminate in the lymphoid aggregation placed at the level of bifurcation of the inferior mesenteric artery.[4] . . . It must not be forgotten, however, that these short trunks come from every region of the rectum. This explains the constant involvement of the nodes placed exactly at the level of bifurcation of the inferior mesenteric artery [4] in cancer of the rectum regardless of 'high' or 'low' location of the lesion. It is in this position that Mondor found the lymph node which, by analogy with the principal node of Küttner in cancer of the tongue, he called the *principle node of the rectum.* Some other collecting trunks, the *middle,* ascend without stopping at the nodes of bifurcation, to a node placed along the inferior mesenteric artery near the point of origin of its lowest sigmoid branch and lastly, Villemin, Huard, and Montagné described the *long* collecting trunks. In the majority of cases this

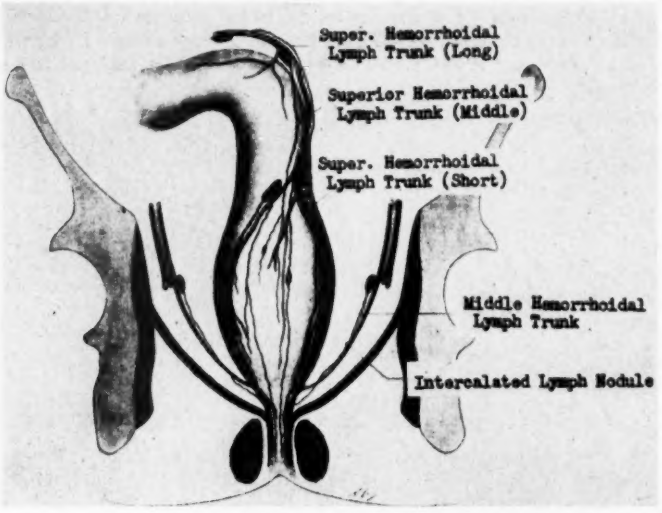
Super. Hemorrhoidal Lymph Trunk (Long)
Superior Hemorrhoidal Lymph Trunk (Middle)
Super. Hemorrhoidal Lymph Trunk (Short)
Middle Hemorrhoidal Lymph Trunk
Intercalated Lymph Nodule

Fig. 3.—Lymph trunks of the rectum (schematic drawing) (Rouvière [3]).

description has reference to a trunk which springs from the lower part of the rectum and terminates in the lymph nodes placed at the summit of the pelvic mesocolon (above the nodes which receive the middle trunks) near the origin of the left colic artery.

These anatomic characteristics of lymphatic drainage of the anal area may be summarized as follows:

1. The lymphatics of the cutaneous part of the anus pass across the perineum, the inguinal crease, inferior pubic region or medial thigh to the superficial inguinal nodes.

2. The cutaneous anal zone may communicate directly with the anorectal nodes through the inferior collecting lymphatic trunks.

3. The hypogastric nodes may be connected directly (or indirectly through an intercalating node on the course of the middle hemorrhoidal blood vessels) with the

4. "According to H. Rouvière the inferior mesenteric artery retains its name to a point opposite the third sacral vertebra . . . *Translator's Note.*"

anal canal through the middle collecting trunks which emerge from the wall of the pars analis recti below or slightly above the insertion of the levator ani muscle.

4. The area of origin for the superior hemorrhoidal trunks extends as low as the anal cutaneous zone and may empty (*a*) into the anorectal nodes, (*b*) into the nodes at the bifurcation of the superior hemorrhoidal artery or (*c*) into the nodes near the origin of the left colic artery.

From this anatomic description it seems apparent that any form of removal of anal carcinoma short of the radical combined abdomino-perineal resection of anus, rectum and lower sigmoid colon is a temporizing measure; that local excision or perineal proctectomy should be regarded as an attempt at palliation and not of cure.

Fig. 4 (Case 26).—Extension of squamous cells and carcinoma in posterior vaginal wall.

And, if radical resection for cure is contemplated, removal of the superficial inguinal nodes must also become an integral part of this radical procedure.

That this apparently radical approach to surgical resection of anal carcinomas may not be wholly adequate is obvious. After surgical extirpation of such a lesion by the combined abdomino-perineal method it is not uncommon for recurrences in the pelvis to appear. In women such recurring carcinomas can often be palpated beneath the posterior vaginal wall. Villemin, Huard and Montagné [5] after injecting the mucocutaneous zone of the anus of three specimens taken from women saw

the lymphatic plexuses of the superior part of the posterior vaginal wall colored and communicating with the small trunks which emerged from the anterolateral portion of the ano-rectal plexus.

5. Villemin, F.; Huard, P., and Montagné, M.: Rev. chir. **63**:39-80, 1925.

They also recalled

that Poirier in studying the peri-uterine inflammatory adhesions expressed the idea that there existed pathological recto-vaginal anastomoses. This opinion was confirmed by Morau who established moreover that these anastomoses were not only pathological but *normal.*

These observations indicate well the imperative need for sacrificing the posterior vaginal wall while carrying out the perineal portion of the combined operation in women.

In men direct communication between the prostatic and seminal vesicle lymphatic plexuses and the rectum is said to exist.[3] This was not seen in the specimens prepared by Villemin, Huard and Montagné.[5] However, Bruhns [6] has described communicating branches from the posterior side of the prostate passing across the anterior and lateral surfaces of the rectum to the posterior surface. These vessels emptied into the chain of nodes along the middle hemorrhoidal vessels.

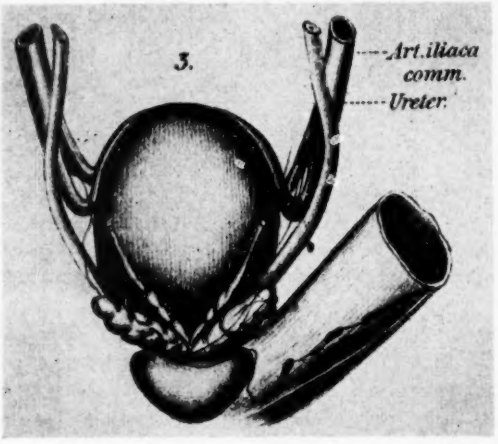

Fig. 5.—Anastomoses between prostate and rectum (Bruhns [6]).

Most surgeons are reluctant to add a one- or two-stage inguinal node dissection to the rigors of a radical combined abdomino-perineal resection. Yet, in the treatment of anal carcinomas, Cattell and Williams [7] have reported that 1 of their 10 patients had inguinal metastases; 4 of the 26 patients (15%) reported by Keyes [8] had inguinal node involvement, and among 48 patients treated by radical operation and reported by Sweet,[9] 16 (33%) had inguinal node metastases at the time of their deaths.

The cutaneous part of the anus is drained on either side by two to five lymphatic trunks which extend in the subcutaneous tissues of the perineum, through the inguinal crease, or along the medial surface of the thigh or in the inferior pubic region and terminate in the superficial inguinal lymph nodes. Semba [10] has even

6. Bruhns, C.: Arch. Anat. u. Physiol., Anat. Abtheilung, pp. 330-348, 1904.
7. Cattell, R. B., and Williams, A. C.: Arch. Surg. **46:** 336-349, 1943.
8. Keyes, E. L.: Ann. Surg. **106:**1046-1058, 1937.
9. Sweet, R. H.: Surg., Gynec. & Obst. **84:**967-972, 1947.
10. Semba, cited by Rouvière, H.[3]

described connections between the anal cutaneous lymphatics and the inferolateral group of the superficial inguinal lymph nodes through the gluteal lymphatic network which lies in the gluteal crease. Since the cutaneous lymphatic network communicates freely from side to side across the median raphe (Fig. 2), there is every likelihood of metastases, when they occur, being bilateral. Thus, when undertaken, inguinal node dissections must be bilateral.

Upon consideration of bilateral groin dissections, thought must be given to the extent of this dissection and to the time at which it may be carried out. The studies of Quénu,[11] Gerota[12] and Poirier and Cunéo[13] indicate that the anal cutaneous lymphatic trunks terminate in the superficial inguinal nodes—whether they end in the medial or lateral group or in the superior or inferior group does not seem to be of particular importance.

Fig. 6.—Superficial lymphatics of the lower extremity; posterior view. (After a preparation by Verge-Brian) (Rouvière[3]).

The value of performing bilateral groin dissections in the presence of known or probable metastases is debatable, but there is accumulated evidence[14] to suggest that cure is still possible even in these circumstances. Under these conditions, of known or probable inguinal metastases, a radical dissection, to include the inguinal femoral and iliac nodes, is indicated.

It is the belief of many surgeons[15] that "elective" groin dissections, in the absence of palpable inguinal nodes or involvement shown on clinical examination,

11. Quénu, E.: Bull. Soc. Anat. **7**:399-409, 1893.

12. Gerota, cited by Rouvière H.[3]

13. Poirier, P., and Cunéo, B.: The Lymphatics, translated by W. T. Leaf, Chicago, Keener and Co., 1904.

14. Pack, G. T., and Rekers, P.: Am. J. Surg. **56**:545-564, 1942

15. Pack, G. T., and Rekers, P.[14] Cattell, R. B., and Williams, A. C.[7]

are constantly indicated for epitheliomas of the anus. Under these circumstances a dissection without extension above the inguinal ligament into the pelvis is all that is required. By this conservatism both groins may be dissected at the same operation. If one group of nodes is involved a bilateral dissection should be undertaken, but the radical type of resection of the inguinal and iliac nodes [14] is required only on the side found to be involved on histological examination.

The time at which such dissections are carried out is of considerable importance. The postulates laid down by Pack and Reckers [14] for successful groin dissections must be given careful consideration. When the primary cancer is cured, controlled or controllable the second stage or groin dissection should be carried out after an elapse of 10 to 14 days after the abdomino-perineal operation. It is Pack and Reckers' [14] belief that the lymph nodes in the groin should remain to exercise their function as filters for cancer cells which may be metastasizing at the time the primary tumor is removed.

A satisfactory theoretical method of surgical treatment based upon the foregoing anatomic outline should embrace the following measures:

1. Radical resection of anus, rectum, and sigmoid colon should be performed. This dissection should include extensive resection of the levator ani muscles and pelvic fascia. A wide removal of the perianal skin should be included.

2. In women, resection of the posterior vaginal wall must be carried out. Routine resection of the prostate and seminal vesicles in men is not so readily acceptable but probably as desirable.

3. In the absence of clinical involvement of the inguinal nodes, "elective," bilateral inguinal node dissection should be done 10 to 14 days after the combined abdomino-perineal operation. (*a*) This dissection is imperative when the primary lesion appears cured or controlled. (*b*) When the primary resection of the lesion has been done for palliation only, "elective" dissection is not indicated.

4. In the presence of unilateral inguinal node involvement, radical resection of the involved inguinal and iliac nodes should be done along with the "elective" resection of the inguinal nodes on the side found to be uninvolved on clinical examination. This may be done at the end of the 14-day interval and may be carried out at a two-stage operation. The inguinal node dissections are indicated only in the face of known or probable cure of the primary lesion.

5. A two-stage, bilateral, radical inguinal and iliac node removal in the presence of histologically found bilateral inguinal metastases is indicated only in the presence of reasonably certain total ablation of the primary tumor.

Since the epitheliomas of the anus do not differ basically from similar lesions occurring in squamous epithelium elsewhere there has been a strong inclination to treat these lesions, as elsewhere, by some form of irradiation therapy. The results of such treatment on 20 patients reported by Bensaude, Cain, Oury and Poirier [16] have been the outstanding example cited in favor of this form of therapy. Eight of their 20 patients are without recurrence after one to 10 years—six patients have been followed two or more years. In eight patients local or distant recurrences have occurred; in the remaining four patients the local lesion itself has not been controlled. In strong contrast Sweet [9] has reviewed 77 patients with epidermoid

16. Bensaude, R.; Cain, A.; Oury, P., and Poirier, P.: Presse méd. **41**:1837-1842, 1933.

carcinoma of the anus and rectum of whom 19 were treated by irradiation therapy, 7 by x-ray and 12 by radium therapy. All but one of these patients are dead. None of the seven patients treated by x-ray therapy lived more than one year. Eleven of the 12 patients treated by radium therapy lived three months to five years. These results are most disappointing but serve as a striking indictment against this form of therapy. The anatomic location of these lesions makes them poor objects even for palliation from irradiation therapy. The degree of pain and tenesmus following extensive irradiation of the perianal skin and the nearby sphincter muscles is great. The irritating anorectal discharge is often profuse, and the slow healing of the lesion and irradiated skin is exceedingly distressing. Once metastases have occurred in the regional lymph nodes the lesion appears no longer amenable to cure by irradiation therapy.

Bacon and his associates [17] have advocated a combined attack upon these neoplasms—surgical extirpation followed by immediate implantation of radon seeds into the stumps of the obturator muscles and the anterior levator muscles. Seventeen of their 26 patients with squamous cell carcinoma are living six months to six years after operation. Four of these patients had inguinal node dissection and three of these are alive seven months to more than five years later. Removal of the posterior vaginal wall in women is strongly advocated.

As a basis for the evaluation of any form of treatment information must be available upon the course and life history of those patients upon whom no definitive curative measure was accomplished. In reviewing those patients seen in the University Hospital since 1934 six patients fit this category.

Case 5 (No. 518266).—The patient was a man aged 64 years with an ulcerating lesion of the right lateral anal wall and severe cerebral arteriosclerosis. There was no enlargement of the regional lymph nodes. Biopsy specimen showed squamous cell carcinoma, grade III. Operation was refused by the patient in January, 1943. He returned in December, 1943, with mild obstructive symptoms; hard, matted nodes in the left groin and extension of the tumor into anal skin. The patient's guardian refused permission for operation because of poor prognosis. The patient died July 28, 1945.

Case 11 (No. 245681).—The patient was a man aged 64 years. He had been under periodic treatment for four years for urethral stricture. An anal lesion was discovered accidentally during digital examination. Histologic examination on Sept. 13, 1944, showed a grade III, squamous cell carcinoma. A rectovesical fistula developed shortly thereafter. The patient died Sept. 27, 1944.

Case 10 (No. 549364).—The patient was a woman 61 years of age. This patient had a seven months' history, at least, of anal pain, tenesmus, bleeding and diarrhea. Laparotomy revealed widespread peritoneal implants of carcinoma and a "frozen" pelvis. Colostomy only was done. The patient died Aug. 25, 1944, two months after her operation.

Case 32 (No. 647684).—A 47-year-old man who gave a history of "hemorrhoids" for many years had symptoms of intermittent bleeding. Prior to his admission to the University Hospital he had developed acute urinary obstruction. His physician, upon rectal examination, had found a neoplastic mass involving at least the anterior half of the anal canal. Biopsy material found this revealed a cornifying squamous cell carcinoma, grade II. Operation on Oct. 20, 1948, revealed invasion of the prostate and right lateral pelvic wall by neoplasm; it was considered unresectable and a proximal colstomy was done. Postoperatively the patient received x-ray therapy; he expired rather suddenly during the course of this therapy. Postmortem examination revealed the carcinoma within the pelvis, carcinoma emboli within the lungs, a large pelvic abscess and active, cavitary pulmonary tuberculosis.

17. Bacon, H. E.; Venturo, R., and Sauer, I.: J. M. Sinai Hosp. **17**:478-485, 1951.

Case 27 (No. 301808).—The patient was a 54-year-old woman with a six months' history of increasing constipation and bleeding through the rectum. Suppository insertion led to the discovery of a nontender mass in the anus. Examination revealed a 6 by 6 cm. mass in the posterior anal canal. This was diagnosed as a medullary squamous cell carcinoma. The patient failed to return for advised therapy but is thought to have had radium implantation in the lesion by her home physician. Verification of this could not be obtained. She died March 30, 1934 one and one-half years later.

Case 31 (No. 361061).—The patient was a 65-year-old man admitted to the hospital for acute urinary retention. He had had hemorrhoids for 30 years. These had protruded, over the past three years, after each bowel movement. About three years ago he had noted "hardness" about the anus, and nine months ago one of the protruding hemorrhoids had become "hard." Ten weeks prior to his visit here he is said to have had two "radium" treatments and injection of the hemorrhoids. This treatment could not be confirmed. On examination there was a large sloughing mass in the anal canal with induration extending 5 to 6 cm. beyond the canal. Inguinal nodes were enlarged and clinically positive. A suprapubic cystotomy done on May 29, revealed neoplasm in the base of the bladder. The patient died June 8, 1935. Necropsy revealed medullary squamous cell carcinoma arising in the anal canal with extension to the rectum, urinary bladder, seminal vesicles and metastatic to the omentum, inguinal, aortic and bronchial nodes, lungs and diaphragm.

Results with No Definitive Therapy

6 Patients	Longest survival, 2½ yr. (Two patients may have had some form of irradiation therapy prior to the examination. This could not be verified and failed to alter their prognosis.)

The least exacting operation and the one usually most acceptable to the patient is local excision. It is tempting when reviewing a group of patients treated in this manner to suggest that "upon selected patients" local excision may be adequate and that wide, radical removal can in no way improve the life expectancy of these particular persons. The difficulty lies, of course, in the means of selection. One's inability to select accurately is well demonstrated in the three patients upon whom this form of therapy was undertaken.

Case 14 (No. 518383).—The patient's case history was given at the beginning of this paper. The period of survival with known carcinoma was six and one-half years after wide local excision.

Case 20 (No. 530393).—The patient was a 58-year-old woman. She had had "hemorrhoids" for five to six years but recently had noted pain in the anal area as well as bleeding. A diagnosis of thrombosed hemorrhoid was made and excision undertaken. Histologic sections of the material removed showed a squamous cell carcinoma, grade II. Wide reexcision, including a portion of the external sphincter, was done. A residual tumor was not found. The patient is alive and well eight years after the operation.

Case 9 (No. 378618).—The patient was a man 77 years of age with a "tumor in the rectum" for two years. Cornifying squamous cell carcinoma was present in a biopsy specimen taken March 23, 1936. The patient refused operation at that time but is reported to have had local excision of the lesion later by his physician. He died Dec. 5, 1940, four years and nine months after the initial histologic diagnosis was made.

Results with Local Excision

1 Patient	Alive and well 8 yr.
2 Patients	Dead; longest survival, 6½ yr.

It is tempting indeed to speculate that long survival in the two patients now dead might have been converted to indefinite survival, without tumor, had a more complete operation been permitted at the time of the initial positive diagnosis.

Experience with irradiation therapy of these neoplasms has been unsatisfactory and little accurate information of the response of the neoplasm to such treatment can be obtained from these patients. Six of the eight patients so treated

had their irradiation treatment on the basis of palliation alone. Two patients, however, are of some interest; one of these (Case 4) was treated by excision and implantation of radon seeds into the base of the excised tumor. This form of therapy was chosen because of the patient's age. Good symptomatic palliation was obtained, but prompt recurrence of the tumor was apparent three months later and a large, exuberant tumor was present upon examination seven months later. Of equal interest is a second patient (Case 18), a 32-year-old woman. Her physician had excised an anal fissure which was diagnosed a basal cell carcinoma. In this histologic diagnosis we concurred, and proximal colostomy and irradiation therapy were undertaken. Adequate regression was not obtained, and radical excision showed this carcinoma

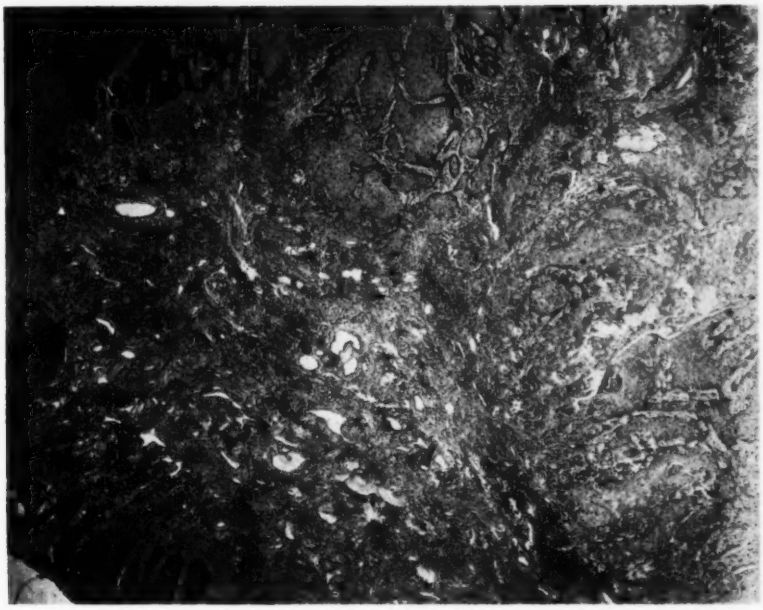

Fig. 7 (Case 20).—Squamous cell carcinoma arising in an external hemorrhoid.

to be a squamous cell lesion, with a basal cell pattern in some areas. Metastasis had occurred to the liver by the time of surgical removal. Of interest also was the presence of a tumor still within the primary lesion after much irradiation therapy. The progress of patients treated by this means is outlined in the following case reports.

Case 2 (No. 496315).—The patient was a man aged 73 years. "Ulcers of the rectum" were excised by his physician nine months previously. Pain was the presenting symptom at that time. Ulceration occurred on the outside of the anus four to five months prior to his first visit to the University of Michigan Hospital. Upon examination a large ulcerating lesion was seen to surround the anus and fixed, bilateral inguinal nodes were present. The biopsy material showed a cornifying squamous cell carcinoma, grade II. Palliative x-ray therapy was given to a single port over the anal lesion. The patient died March 19, 1942, two months after completion of his treatment.

CASE 4 (No. 506410).—The patient was a woman 81 years of age with rectal bleeding for two years. This was diagnosed by her physician as "piles" and treated with salves. Upon examination a neoplastic mass was found to be present over the posterior half of the anal wall. There was no inguinal node enlargement. Because of the advanced age of the patient electrocautery excision of the lesion was done and radon seeds implanted. The patient died April 14, 1944, 22 months after the operation and irradiation therapy. Excellent palliation was obtained for about one year.

CASE 16 (No. 564366).—The patient was a woman aged 55 years. Symptoms of weight loss and rectal bleeding had been present for one year. A completely encircling neoplasm was present in the anal canal. It was a medullary, grade III carcinoma arising from squamous epithelium. The pelvic adnexa appeared fixed. Operative removal was considered unwise and irradiation therapy undertaken as a palliative measure. The patient died May 16, 1945, two months after completion of her treatment.

CASE 18 (No. 518208).—The patient was a 32-year-old woman. Pain in the anal area, bleeding and constipation had been present one and one-half years when she was first seen. One month prior to admission an operation upon an anal fissure was carried out by the patient's physician and this material was diagnosed carcinoma. The initial diagnosis was basal cell carcinoma. A proximal colostomy followed by x-ray therapy to two gluteal, two subgluteal and one perineal field was undertaken. Good regression was obtained but residual tumor was left. A combined abdomino-perineal resection was done on May 13, 1943. At this time the lesion was considered a grade II squamous cell carcinoma which in areas showed a basal cell pattern. No lymph nodes contained carcinoma and a node from the left groin was negative for carcinoma. However, a 3 cm. nodule was present in the left lobe of the liver. The patient died Aug. 16, 1943.

CASE 24 (No. 135605).—The patient was a 70-year-old woman with intermittent rectal bleeding for 40 years. This was attributed to hemorrhoids. One month prior to admission a severe rectal hemorrhage occurred. The lesion surrounded the anterior two-thirds of the anal canal and was a medullary squamous cell type. As a result of the patient's age and general debility irradiation therapy was elected. The patient died on Jan. 16, 1935 during the course of this therapy.

CASE 28 (No. 337912).—A 53-year-old man had initial symptoms of constipation and bleeding; six months later a mass appeared next to the anal canal. The anal canal was surrounded by neoplasm which produced an ulcerating mass on the right, outside the canal. In the right groin was a large ulcerating, neoplastic mass. The neoplasm, on biopsy, from both anus and groin, showed minimal cornification. July 9, 1934 radium was inserted into the neoplasm within the canal and about that in the right buttocks. Shortly after this external irradiation therapy was undertaken and was given in three courses at two-month intervals. He died May 12, 1935. Prior to his death severe hemorrhage occurred from the groin wound.

CASE 30 (No. 578288).—A man of 77 years had had hemorrhoids for 25 years. These are said to have bled consistently over this period. More recently diarrhea, weakness and anal incontinence appeared. Upon examination there was a neoplastic mass involving the anterior one-half of the anal canal which extended anteriorly over the perineum almost to the base of the scrotum. Removal of an enlarged left inguinal node was done. There was no carcinoma present within it. The anal lesion showed a cornifying squamous cell carcinoma, grade II. Because of the extensive perineal involvement irradiation therapy was undertaken. Radium needles were implanted on March 29, 1946, but these were dislodged by the patient and the amount of radiation delivered indeterminate. External irradiation undertaken shortly, but after the administration of 2600 r over the lesion the treatment was interrupted to treat the patient's acute urinary retention. Therapy was never resumed. The patient died Oct. 8, 1946, three months after discharge.

CASE 19 (No. 611808).—The patient was a man of 57 years of age. There had been a lump in the anal region for at least nine months, intermittent bleeding for seven months, moderate pain and a 73 lb. weight loss. There was a 4 cm. ulcerating mass outside the anal orifice and this extended to the scrotum. There were hard inguinal nodes on the right. Biopsy of the lesion

showed a squamous cell carcinoma, grade III. The lesion was considered nonresectable; a transverse colostomy was done and 3000 r of x-ray given to the perineal lesion. The patient died Dec. 15, 1948, 20 months after completion of his therapy.

Results with Irradiation Therapy
8 Patients Longest survival, 22 mo.

The combined operation which undertakes removal of the sigmoid colon, rectum and anus through both the abdominal and the perineal route is ordinarily considered a radical method of removal of these structures and as such is frequently sufficient when used for the commoner adenocarcinoma. That it is less likely to succeed when one is dealing with a squamous cell carcinoma arising at the lower end of this same tract is apparent from the following case histories.

CASE 3 (No. 511441).—A woman aged 42 years had abdomino-perineal resection for squamous cell carcinoma of the anal canal in September, 1942. The lesion was initially detected when carcinoma was found in a rectovaginal fistula. The inguinal nodes were negative, clinically, prior to operation. Recurrence in the perineum appeared one year postoperatively and was treated with radium. The perineal lesion recurred and progressed. In June, 1944, the right inguinal node was found on clinical examination to be positive. A chorodotomy was performed in December, 1944. Death occurred in March, 1946.

CASE 6 (No. 582382).—The patient was a woman aged 65 years who had had abdomino-perineal resection Dec. 19, 1945. The inguinal nodes were small. Nodes removed from the groins were negative for carcinoma before operation. The vaginal wall was not removed. A cautery excision of recurrent carcinoma invading the posterior vaginal wall was done May 6, 1946. Death occurred on Feb. 18, 1947, of recurrent carcinoma in the perineum with extension and invasion of the urinary bladder.

CASE 7 (No. 358341).—The patient was a man aged 65 years who had had abdomino-perineal resection on April 30, 1935. The inguinal nodes were negative according to clinical examination prior to operation. The patient died 36 hours after operation of acute pulmonary edema, pulmonary fat embolism and acute right heart failure. No evidence of residual carcinoma was detected in the postmortem examination.

CASE 8 (No. 506813).—The patient was a woman aged 58 years. This patient had a combined abdomino-perineal resection of her anal carcinoma on June 30, 1942. The posterior vaginal wall was removed at this operation. Because of an enlarged lymph node in the right groin, removal of the node was done at this operation. This contained metastatic squamous cell carcinoma. A large growth recurred in the groin in 1946. The patient was bedridden after July, and died November 14.

CASE 12 (No. 445757).—The patient was a man aged 68 years. He had had sigmoid colostomy perineal proctectomy and one year later abdominal resection of the sigmoid colon for squamous cell carcinoma in the anal canal. The last operation was Oct. 4, 1940. Peritoneal carcinomatosis was present at the last operation. There was no evidence of intra-abdominal metastases at the time of sigmoid colostomy. The patient died December 28 of carcinomatosis.

CASE 13 (No. 441599).—The patient was a woman aged 42 years who had combined abdomino-perineal resection on April 21, 1939 for squamous cell carcinoma of the anal canal. The posterior vaginal wall was removed. The inguinal nodes were not considered clinically positive and none were removed for examination. The patient died March 1, 1943, "after suffering for a year with cancer in the hip and leg."

CASE 15 (No. 316709).—The patient was a man aged 61 years, who had been seen on many previous occasions with a low-lying rectal polyp. Between 1933 and 1952 four attempts had been made to eradicate this lesion. At the time of its fifth recurrence a squamous cell carcinoma was seen infiltrating these tissues. A combined abdomino-perineal resection was done on Feb. 22, 1952. After the operation the patient had a small pulmonary embolus. An x-ray taken at this

time revealed not only an area of probable infarction but multiple, nodular pulmonary lesions which were thought to be metastatic. Death occurred on May 15, 1952. Necropsy examination revealed metastatic carcinoma in the pelvis, liver and lungs.

CASE 21 (No. 599737).—The patient was a man aged 56 years who had had combined abdomino-perineal resection for squamous cell carcinoma of the anus on Oct. 8, 1946. Enlargement of right inguinal nodes prompted biopsy examination of these preoperatively. No metastatic carcinoma was found there. However residual neoplasm was left attached to the anterior wall of the sacrum. The patient died in another hospital on March 1, 1948 with metastatic cancer in the liver.

CASE 22 (No. 590042).—The patient was a woman of 59 years admitted because of an unhealed anal fissure which had been operated upon six months earlier by her physician. A combined abdomino-perineal resection was done on May 8, 1946. No metastatic carcinoma was found in the regional nodes of the operative specimen and no clinically positive inguinal nodes were noted. The posterior vaginal wall was not removed. The patient is alive and well seven years after operation.

CASE 23 (No. 680932).—The patient was a 60-year-old man who had combined abdomino-perineal resection on May 8, 1950 for a squamous cell carcinoma apparently arising in an anal fissure. The fissure had failed to heal in five months after an operation by his physician. There was lateral inguinal adenopathy, with the larger node, 3 by 1 cm., on the left. The patient died on his sixteenth postoperative day of acute cardiac failure with pulmonary edema. No residual neoplasm was discovered on postmortem examination. The inguinal nodes were not examined.

CASE 25 (No. 574986).—The patient was a woman of 46 years of age. She had combined abdomino-perineal resection Aug. 20, 1945. Hemorrhoidectomy had been done on two occasions by her physician within three months of admission without relief of symptoms. The posterior vaginal wall was ulcerated and was widely removed. The inguinal nodes were not involved, as found by clinical examination. The patient was admitted to a mental hospital in 1947. Here a carcinoma of the breast was found and removed. She died in this hospital Oct. 31, 1950, from "hemorrhage of the bowel, secondary to carcinoma of the bowel."

CASE 26 (No. 597579).—The patient was a 65-year-old woman who had abdomino-perineal resection of squamous cell carcinoma on the antero-lateral wall of the anus on Sept. 3, 1946. The enlarged right inguinal node removed preoperatively revealed no carcinoma. A large portion of the posterior vaginal wall was removed in the dissection. The patient was alive and well seven years after operation.

CASE 29 (No. 633587).—The patient was a man 67 years of age. He had squamous cell carcinoma in the fistulous tract removed by abdomino-perineal resection on March 26, 1948. A residual tumor was left at the base of the prostate and in the region of the right seminal vesicle. The patient died of carcinoma Dec. 16, 1948.

CASE 36 (No. 668440).—The patient was a Negro woman 49 years of age with wide invasion of the perineum by squamous cell carcinoma. There was a recto-vaginal fistula. An enlarged right inguinal node showed metastatic carcinoma. Combined abdomino-perineal resection of the anus and rectum, total cystectomy, vaginectomy and removal of cervical stump was done on Oct. 18, 1949. The patient died of carcinoma December 21.

Results with Combined Abdomino-Perineal Resection

2 Patients	Died from operation
4 Patients	Inguinal node metastases at death (*a*) Probable—Cases 3 and 13 (*b*) Proved—Cases 8 and 36
1 Patient	Recurrence in perineum (vaginal wall not removed)
3 Patients	Known residual tumor left at operation
1 Patient	Known pulmonary metastases
1 Patient	"Cancer" death; site not known
2 Patients	Alive and well
Total 14 Patients	

Efforts to amend these generally poor results were made in several directions. In five patients inguinal and, where indicated, iliac node dissections were done, in addition to combined resection of the primary lesion. In one of these patients it seems likely that the residual tumor remained in the pelvis (Case 35), and in another, in addition, widespread dissemination occurred with metastatic lesions in lungs and bone.

None of the patients who has apparently benefited from this form of therapy has lived long enough to present unequivocal evidence of cure. Moreover, it is of interest that in none of the three remaining patients was a tumor present in the inguinal nodes examined after the dissection. If this observation is valid, the node dissection was an unnecessary operation or the histological examination was not sufficiently complete to detect whatever small foci of metastatic cells were present.

CASE 33 (No. 744146).—The patient was a 50-year-old Negro woman with a one year history of anal discomfort, bleeding and constipation. On the left lateral wall of the anal canal was a 2 by 2 by 1 cm. firm friable mass. Some 20 years ago a para-anal abscess had been incised and drained in this general area. The lesion was a medullary squamous cell carcinoma. A combined abdomino-perineal resection was done on Jan. 23, 1953. Bilateral complete femoral node dissections were done on February 20. No neoplasm was found in the nodes on either side. The patient is alive and well.

CASE 34 (No. 726601).—The patient was a 52-year-old woman who had had a hemorrhoidectomy 10 years ago but had had occasional bright red rectal bleeding since. Tenesmus was noted recently. A routine physical examination revealed a 2 cm. polypoid lesion in the posterior anal wall with minimal adjacent involvement. Histologically this was a medullary squamous cell carcinoma. A combined abdomino-perineal resection was done on May 5, 1952. The vaginal wall was not removed. Two of the regional lymph nodes showed metastatic carcinoma. A bilateral complete femoral node dissection was done on June 11. No metastatic carcinoma was present in these nodes. The patient is alive and well.

CASE 35 (No. 660297).—The patient was a 45-year-old woman with a history of five months of constipation and rectal bleeding followed shortly by the finding of a mass just anterior to the anus. Examination showed a large mass in the anterior anorectal wall which extended to but did not ulcerate the posterior vaginal wall. According to histological examination this was a grade III squamous cell carcinoma. A combined abdomino-perineal resection with removal of the posterior vaginal wall was done on May 19, 1949. The majority of both rectal and sigmoid lymph nodes showed metastatic carcinoma. On September 12 a complete bilateral femoral node dissection was done. Carcinoma was present in one node according to results of dissection of the right side so that on October 14 a right iliac node dissection was done. No neoplasm was noted in this specimen. The patient was next seen in August, 1950, with pain in the lower part of the spine, the right side and in the perineum. There appeared to be recurrent neoplasms in the right groin and vagina. Both showed recurrent carcinoma on histologic examination. On Sept. 1, 1950, cordotomy was done for intractable pain. The patient died Nov. 1, 1951.

CASE 37 (No. 648210).—The patient was a 51-year-old woman with a noncornifying squamous cell carcinoma in the anterior half of the anal canal. The lesion had been present for at least nine months and there had been an operation upon it four months before. On Oct. 29, 1948, a combined abdomino-perineal resection was done. At the operation the entire posterior vaginal wall was removed. On November 23 bilateral inguinal node dissections were done. There was involvement of many lymph nodes in the anorectal specimen, but none of the inguinal nodes showed carcinoma. The patient died December 21 with carcinoma in the lungs, a frozen pelvis and probable metastatic carcinoma in the bone of the right hip.

CASE 1 (No. 609546).—The patient was a 62-year-old woman whose symptoms were present for at least eight months. Biopsy of the lesion on the postero-lateral anal wall showed a minimally cornifying squamous cell carcinoma. A combined abdomino-perineal resection of anus, rectum

and posterior vaginal wall was done on March 1, 1947. None of the isolated lymph nodes contained carcinoma. On March 18, groin dissection was done. Again no positive nodes were identified. The patient died June 28, 1948, without evidence of recurrence of the neoplasm.

Results with Combined Abdomino-Perineal Resection—Inguinal and Iliac Node Dissection

2 Patients	Alive and well (5 and 13 mo.)
1 Patient	Dead; no carcinoma
2 Patients	Dead of recurrent carcinoma
Total 5 Patients	

Two additional reports of patients must be added to complete the roster of this group of patients with squamous cell carcinoma of the anal canal.

CASE 17 (No. 674961).—This patient was a 59-year-old man. Two years prior to his first visit he had noted protruding hemorrhoids. One and one-half years ago he noted perianal pruritus and one year ago pain and bleeding after bowel movement. In July, 1949, biopsy examination of the area by his physician revealed a squamous cell carcinoma and a course of x-ray therapy was given. Pain following bowel movements returned in November, 1949. When first seen at the University of Michigan Hospital no definite tumor was present but much irradiation reaction was present in the perianal skin. Extensive biopsies of the treated site were negative for neoplasm. The original biopsy specimen was diagnosed as minimally cornifying squamous cell carcinoma. Examination revealed bilateral inguinal node enlargement. The nodes on the right were considerably larger and firmer and readily suggested the presence of metastatic neoplasm. On Feb. 2, 1950, a right inguinal and iliac node dissection was done. Practically all of the nodes isolated had been replaced by neoplasm. On May 9 a left inguinal and iliac node dissection was done. Three of the 27 isolated nodes from this dissection had been replaced by carcinoma. The patient did well for approximately one year and was able to return to work. He returned in May, 1952, with marked edema of the thighs and genitalia which has progressed to date. In addition he now has a metastatic carcinoma over the left pubic tubercle and pulmonary changes suggestive of metastatic carcinoma.

CASE 38 (No. 564350).—This patient was a 75-year-old man first seen Feb. 20, 1945. Six years and one year prior to this time he had had hemorrhoidectomies because of painful, protruding hemorrhoids. He continued to have rectal pain and bleeding upon defecation and pruritus ani. Because of symptoms of the upper gastrointestinal tract a survey of the stomach was undertaken and a lesion suggesting carcinoma of the stomach was found. A subtotal gastrectomy was done on March 4. A chronic peptic ulcer of the pylorus was found. The patient had an excellent convalescence and was seen upon six occasions as an outpatient between the date of discharge in 1945 and March 1950. At this time a slightly tender palpable mass 3 by 2 cm. in diameter was noted in the left groin. Biopsy of this was delayed until April, 1950. Histologically this was a cornifying squamous cell carcinoma in the lymph nodes. Only upon close questioning did this elderly man recall that his physician had removed a "tumor" from the anus in September, 1949. Examination of the histological section obtained from the physician revealed this lesion to be a cornifying squamous cell carcinoma, grade II. Repeated biopsy specimens from this area failed to reveal residual tumor. On April 25, 1950, a dissection of the inguinal and iliac nodes was done. Several of these nodes contained metastatic squamous cell carcinoma. Postoperatively there was much pain and rehabilitation was prolonged and difficult. He died November 15. His death was attributed to carcinoma though precise evidence of this is lacking.

Evaluation of these two patients is difficult. Evidence to date suggests that their primary lesions had been controlled and metastases to the inguinal and iliac areas resulted in tumors, which were well beyond the confines of the subsequent operation. It is also recognized that metastases into the regional hemorrhoidal or colic nodes may have contributed to the widespread nature of these subsequent metastatic foci, although palpable evidence of neoplasm in these areas was not in evidence.

The most outstanding discrepancy in the entire group of patients, both alive and dead, has been the extreme variation in length of survival regardless of the type of

treatment used. This statistical discrepancy, as in the treatment of other neoplasms, should detract in no way from a logical, well planned, courageous attempt to cure these patients.

While it is incorrect to assume that a more determined, perhaps more radical surgical approach would have increased the life expectancy in all of these patients, it is apparent that recurrences and later metastases followed a definite pattern in all. Recurrent neoplasm after combined abdomino-perineal resection reappeared either locally where inadequate removal of anal skin, levator muscle and fascia and other adjacent structure was done, or in relation to the posterior vaginal wall in women in whom this structure was not removed, or in the inguinal and iliac areas. Residual tumor in the male patients was commonly seen to involve prostate and seminal vesicles. It appears reasonable, therefore, that if these structures could have been more successfully removed more of the patients would have had longer survival or better palliation or cure.

In no instance did patients treated by combined surgery and irradiation therapy benefit more than did those treated by surgery alone.

SUMMARY AND CONCLUSIONS

Squamous cell carcinoma arising in the anal canal and perianal skin affords the patient a much poorer chance of cure than does the gland cell carcinoma arising only a few centimeters above this level. It is true that the incidence of this lesion is small. Harvey [18] reviewed 37 cases collected over a period of 27 years; Cattell and Williams [7] have discussed 10 patients who have been observed in their clinic within a period of at least 11 years. Raiford,[1] in 1933, analyzed the findings on 10 patients which had been accumulating since 1908, a period of 25 years and Buie and Brust [19] have published their analysis of 51 patients seen during a period of 13 years.

The group of 77 patients reported by Sweet [9] is one of the largest yet recorded by any single author. Yet, in spite of these and several other [20] excellent analyses and the resulting conclusions for improvement of the lot of this group of patients with squamous cell anal carcinoma, no profound change in prognosis has been affected.

To consider a radical resection of the rectum and anus alone as a wholly adequate means of totally eradicating this type of neoplasm appears unjustified. This is evident after careful consideration of the anatomic peculiarities implied by the location of a neoplasm in this area. After consideration of these characteristics the following surgical measures are suggested: (1) radical resection of the anus, rectum, and sigmoid colon with extensive resection of the perianal skin, levator ani muscles and pelvic fascia; (2) wide resection of the posterior vaginal wall and commissure in the female patient; (3) bilateral inguinal node dissection, in the absence of clinical inguinal node involvement, 10 to 14 days after resection of the primary lesion, and, (4) radical resection of the inguinal and iliac nodes when clinical involvement of these nodes is apparent. Inguinal node dissections are indicated only when the primary lesion is cured or controlled and when no evidence of distant metastases is present.

18. Harvey, H. D.: Ann. Surg. **124**:245-251, 1946.

19. Buie, L. A., and Brust, J. C. M.: Journal-Lancet **53**: 565-571, 1933.

20. Gabriel, W. B.: Proc. Roy. Soc. Med. **34**:139-160, 1940. Keyes, E. L.[8] Rosser, C.: South. M. J. **28**:527-528, 1935. Kerr, J. G.: Texas J. M. **36**:548-551, 1940-1941.

In general one has the impression that length of life in these patients was as long when no definitive form of therapy was used as it was when irradiation therapy was given in palliation. This is to be expected, of course, when long survival may be predicated upon the life span of a few patients with early or small lesions who refuse or fail to accept the form of therapy advised and thus remain untreated. Nevertheless, it does appear in this series that good palliation, in the sense that it is usually attained from irradiation therapy in squamous cell carcinoma elsewhere in the body, was not well approximated in these lesions of the anal canal.

The results in the group of patients upon whom the combined abdomino-perineal removal of the tumor alone was done have been most disappointing. The two patients now alive are both women and it is interesting to note that in one the tumor lay on the anterior anal wall and in this patient a generous segment of the posterior vaginal wall was removed; in the other patient the tumor lay posteriorly and the vaginal wall was not sacrificed. The same observation can be made on the two patients upon whom, in addition to the combined abdomino-perineal removal, inguinal node dissections were done and who are now alive without evidence of recurrence. The validation of this observation in the last two patients, however, will require further time since their period of survival since operation is short. Our experience with inguinal and iliac node dissection after the appearance of nodes in these areas which suggest, according to clinical examination, the presence of metastic carcinoma within them, does not favor this plan of expectant treatment.

MANAGEMENT OF REMAINING COMMON DUCT STONES BY VARIOUS SOLVENTS AND BILIARY FLUSH REGIMEN

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THE PROBLEM of the remaining common duct stones attains considerable significance when one is confronted with the necessity of advising another operation to a patient who has just undergone a recent major surgical procedure. An alternative nonoperative program that offers equal or better results is therefore highly desirable, particularly when one considers the increased morbidity and mortality rates associated with secondary operations on the biliary tract. The purpose of this investigation was to develop a regimen with an effectiveness that would warrant its use in this all too frequent problem in which postoperative choledochograms demonstrate the presence of remaining common duct stones. This report concerns the investigation of 113 solutions tested for their solvent action on gall stones and the effect of the most efficient agents on ductal and liver tissue. An improved, simplified biliary flush regimen is also presented.

The reports on the incidence of cholelithiasis in the general population vary. Probably locality, living conditions, and food habits play a significant role. We estimate that 10 to 30% of the adult population have cholelithiasis. Crump,[1] in his thorough study of 1,000 consecutive necropsies, reported a 32% incidence of cholelithiasis. Of the total number with stones in the gall bladder, 24% had stones in the common or hepatic ducts. Pribram[2] has stated that an average of 20% of patients undergoing choledochostomy later have evidence of remaining common duct stones. Hicken and associates[3] are of the opinion that 95% of the secondary

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1. Crump, C.: Incidence of Gallstones in Gallbladder Disease, Surg., Gynec. & Obst. **53**:447, 1931.

2. Pribram, B. O. C.: New Methods in Gallstone Surgery, Surg., Gynec. & Obst. **60**:55, 1935.

3. Hicken, N. F.; Stevenson, V. L.; Franz, B. J., and Crowder, E.: Technique of Operative Cholangiography, Am. J. Surg. **78**:347, 1949.

operations on the common duct are for elusive stones overlooked at the first operation. One of us (R. R. B.) [4] has shown that 7% of patients with cholelithiasis have stones in the liver ducts. Weiss [5] reports an incidence of 8%.

Strohl, Diffenbaugh, and Guynn [6] analyzed 25,807 reported operations for cholecystitis. The common duct was explored in 23% and the incidence of common duct stones according to the reports varied between 4.2 and 36.8%. This apparent wide variation emphasizes the need for an efficient nonoperative technique for the management of remaining common duct stones. We estimate that 20 to 25% of patients with cholelithiasis have choledocholithiasis or hepatolithiasis.

The condition of the patient, obese, poor risk, with marked edema and adhesions in the area, or imbedded calculi; inadequate light; exposure or anesthesia; anomalous ductal and vascular patterns, and the skill of the surgeon certainly all materially contribute to the incidence of remaining common duct calculi. Delay in diagnosis and delay in operation for cholelithiasis undoubtedly play a significant role in the incidence of choledocholithiasis.

The nonoperative management of the retained calculus can be classified under these headings: (1) the physiologic biliary flush with hydrocholeretics; (2) administration of solutions for solvent and fragmentation action on stones, and (3) use of sphincter relaxants and anesthetics. These may be used separately or, as is commoner, in combination. A T-tube or catheter in place is required if solvent solutions and topical anesthetics are to be used.

There are three basic types of calculi found in the biliary tract—cholesterol, bilirubin pigment, and calcium. Mixed stones may consist of any combination of these substances.

The majority of calculi of gall bladder origin have a large cholesterol component. Those not of gall bladder origin are chiefly bilirubin pigment, according to Phemister, Aronsohn, and Pepinsky [7] and Carter and associates.[8]

Best and Hicken [9] have demonstrated the flushing action of the biliary tree through the use of dehydrocholic acid products, such as Decholin. With increase in the quantity and the pressure of bile flow through the biliary ductal system, plus sphincter-relaxing agents, calculi, and debris may be washed out of the ductal system into the duodenum. With a T-tube in place, any stones revealed by choledochograms may be further attacked by a solvent solution.

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5. Weiss, S.: Diseases of the Liver, Gall Bladder, Ducts and Pancreas: Their Diagnosis and Treatment, New York, Paul B. Hoeber, Inc., 1935, p. 719.

6. Strohl, E. L.; Diffenbaugh, W. G., and Guynn, V.: Symptoms of Common Duct Stones: Analysis of Clinical Data on 165 Patients Having Explorations of the Common Duct, A. M. A., Arch. Surg. **64**:788, 1952.

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8. Carter, R. F.; Greene, C. H.; Twiss, J. R., and Hotz, R.: The Etiology of Stones in the Common Bile Duct, Arch. Surg. **40**:103, 1940.

9. (*a*) Best, R. R., and Hicken, N. F.: Non-Operative Management of Remaining Common Duct Stones, J. A. M. A. **110**:1257, 1938. (*b*) Best, R. R.: The Quantitative and Qualitative Control of Bile Flow and Its Relation to Biliary Tract Surgery, Ann. Surg. **128**:348, 1948; (*c*) Operative and Non-Operative Methods in the Management of Common Duct Lesions, Minnesota Med. **31**:192, 1948.

The use of chemicals for their solvent and fragmentation action on gallstones dates back to 1891, when Walker [10] instilled ether into a cholecystostomy sinus tract. He was successful in removing an impacted cystic duct stone in a young woman by this procedure. Pribram [11] has investigated the solvent and fragmentation potential of ether more intently perhaps than anyone else to date. He employs a catheter rather than a T-tube. It is his opinion that the expansion pressure of ether results in a spastic sphincter and this neutralizes the expulsive effect. He reports 51 cases without a failure and emphasizes the rewards of persistence in the program. Many other authors [12] have successfully used ether to rid the common duct of a retained stone. Michel [13] and Walters and Wesson [14] feel that the pressure caused by the high volatility of ether promotes expulsion of stones. Burgess [12a] believes that this pressure may cause liver damage. Probstein and Eckert [15] observed toxic effects in dogs from the instillation of ether through cholecystostomy tubes. Amsterdam and Sterling,[16] however, disagree with this opinion as they had a patient instill ether through his T-tube daily for 11 months. Raffl [17] is in agreement with the latter group as long as the pressure is not sustained over too long a period. Boyce [18] feels that ether is safe.

We have followed 73 patients who were subjected to ether or ether-alcohol instillations by us or by immediate colleagues. In only one case could we say that there was a reaction of any great concern. In this particular patient, six ether-alcohol instillations were carried out over an eight-week period before the retained calculus was broken up. The amount of bile flow, which had diminished in quantity and was pale in color, increased along with the patient's strength after a few days of treatment directed toward improving liver function. The patient is well now four years later.

Other solutions than ether have been studied for their solvent effect on gallstones. Goldman, Jackman and Eastman [19] reported that Solution G, a citrate combination, probably had no solvent action, its effect being primarily mechanical.

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10. Walker, J. W.: The Removal of Gallstones by Ether Solution, Lancet **1**:874, 1891.

11. Pribram, B. O. C.² Pribram, B. O. C.: Ether Treatment of Gall-Stones Impacted in the Common Duct, Lancet **1**:1311, 1939; The Method for Dissolution of Common Duct Stones Remaining after Operation, Surgery **22**:806, 1947.

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14. Walters, W., and Wesson, H. R.: The Fragmentation and Expulsion of Common Duct Stones into the Duodenum Using Ether and Amyl Nitrite, Surg., Gynec. & Obst. **65**:695, 1937.

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16. Amsterdam, G. H., and Sterling, J. H.: Conservative Therapy of Residual Calculi Following Operations on the Common Bile Duct: Report of 2 Cases, Ann. Surg. **128**:30, 1948.

17. Raffl, A. B.: Experimental Studies of the Solvent Action of Ether on Gallstones, Am. J. Surg. **52**:65, 1941.

18. Boyce, F. F.: Hepatic and Biliary Tract Disease: Review of Recent Significant Advances, Ann. Surg. **109**:351, 1939.

19. Goldman, B.; Jackman, J., and Eastman, R. H.: Management of Postoperative Choledocholithiasis: Another Use for Solution G, Surg., Gynec. & Obst. **81**:521, 1945.

Strickler and associates [20] also found that this solution was ineffective in dissolving gall stones. The same authors studied dog bile, ox bile, Caroid and sodium taurocholate, with similar results.

Narat and Cipolla [21] investigated the potential of chloroform. They felt that there were several advantages of chloroform over ether: (1) The boiling point of chloroform is 61 C. (141.8 F.) while that of ether is 35 C. (95 F.); (2) the solvent action of chloroform is greater than that of ether; (3) bile pigments are easily soluble in warm chloroform and only slightly soluble in ether, and (4) the solubility factor of chloroform is much greater when the chloroform is warm. They found no demonstrable change in the liver, gall bladder, or biliary ducts of dogs into which they instilled chloroform. It was their conclusion that the use of chloroform was potentially dangerous and should be restricted to the time of surgery. Whipple and Smith [22] were able to diminish bile salt output in dogs by oral administration of small amounts of chloroform. There was no ill effect clinically, normal bile salt output returning in five to seven days. Goldschmidt, Vars, and Ravdin,[23] Miller and Whipple [24] and Whipple and Smith [22] found that protein protected the liver from damage. In the dogs that we killed there was little histologic evidence of liver or ductal damage definitely attributable to chloroform.

In a search for a more effective program, Butsch, McGowan, and Walters,[25] Doubilet and Colp,[26] McGowan, Butsch, and Walters,[27] Bergh,[28] and Best [29] found that glyceryl trinitrate and amyl nitrite promoted sphincter relaxation. The former was found to act more slowly and last longer than the more quickly acting but shorter-lasting amyl nitrite. Doubilet and Colp [26] and Best [29] found that magnesium sulfate relaxed the sphincter but the effect was not too great.

Another approach to the problem of sphincter spasm was through the instillation of topical anesthetics through a T-tube. Glenn and Hill [30] successfully used

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20. Strickler, J. H.; Muller, J. J.; Rice, C. O., and Baronofsky, I. D.: Nonoperative Treatment of Retained Postoperative Common Duct Stones, Ann. Surg. **133**:174, 1951.

21. Narat, J. K., and Cipolla, A. F.: Fragmentation and Dissolution of Gallstones by Chloroform, Arch. Surg. **51**:51, 1945.

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28. Bergh, G. S.: The Sphincter Mechanism of the Common Bile Duct in Human Subjects: Its Reaction to Certain Types of Stimulation, Surgery **11**:299, 1942.

29. Best, R. R.; Hicken, N. F., and Finlayson, A. I.: The Effect of Dehydrocholic Acid upon Biliary Pressure and Its Clinical Application, Ann. Surg. **110**:67, 1939. Best, R. R.[9b]

30. Glenn, W. R., and Hill, W. H.: Common Duct Obstructions Relieved by Injections of a Topical Anesthetic into T Tube, South. Surgeon **14**:3, 1948.

20 cc. of 1:500 dibucaine (Nupercaine) hydrochloride and a similar amount of 1.5% piperocaine (Metycaine) hydrochloride. Harris and Marcus [31] employed 1:500 or 1:1,000 dibucaine hydrochloride with good results.

METHOD OF STUDY

Types of Solutions.—The purpose of this investigation was to study the solvent action of various types of solutions upon gall stones. Table 1 is a classification of these solutions based on their chief chemical characteristics.[32]

Because of the high cholesterol content of the great majority of gall stones, the fat solvents were expected to be quite effective. The surface-tension-lowering agents were studied because of their promise of aiding absorption of the solution

TABLE 1.—*Classification of Solutions*

1. Fat solvents tested
   a. Chloroform
   b. Ether
   c. Ether-alcohol
   d. Alcohol
2. Surface tension lowering agents
   a. Detergent—sorethytan (20) monooleate (N. N. R.); polysorbate (U. S. P.) (Sorlate)
   b. Bile salts
   c. Bile acids
   d. Dog bile and ox bile
3. Calcium-binding agents
   a. Tetrasodium ethelenediaminetetraacetic acid (Versenes)
   b. Citrates
4. Naturally occurring fatty acids
   a. Saturated:
      (1) Caprie (4) Myristic
      (2) Caprylic (5) Palmitic
      (3) Lauric (6) Stearic
   b. Unsaturated:
      (1) Linoleic (3) Oleic
      (2) Linolenic (4) Ricinoleic
   c. Hydroxy fatty acids:
      (1) Ricinoleic
5. Hydrotropic agents
   a. Bile salts
   b. Bile acids
   c. Dog and ox bile
6. Enzymatic agents (hydrolytic)
   a. Trypsin (Tryptar)
   b. Hyaluronidase (Wydase)
   c. Caroid
7. Dispersing agents
   a. Lignin sulfonic compound (Marasperse)
8. Miscellaneous
   a. Strong acids:
      (1) Nitric acid
      (2) Hydrochloric acid
   b. Weak acids:
      (1) Acetic
      (2) Glacial acetic
   c. Boiling water

into the calculus, thus promoting more rapid dissolution. Calcium binding agents were tried because of the varying calcium content of some gall stones. The principle of a chelating agent is that of changing the equilibrium between insoluble calcium salts and calcium ions. This results in removal of the calcium ion, thus converting a hard stone to a soft stone. This type of agent was included because of the known difficulty in breaking up calcium-containing stones. The fatty acids were studied because of the promising effect of lauric acid in preliminary trials. The exact reason for their action was not definitely known. However, it was believed that they might lower surface tension. Enzymes were employed for their possible

31. Harris, F. I., and Marcus, S. A.: Common Duct Stone Relieved by Injections of Nupercaine Solution into T tube, J. A. M. A. **131**:29, 1946.

32. Best, R. R.; Rasmussen, J. A., and Wilson, C. E.: An Evaluation of Solutions for Fragmentation and Dissolution of Gallstones and Their Effect on Liver and Ductal Tissue, Ann. Surg., to be published.

Strickler and associates [20] also found that this solution was ineffective in dissolving gall stones. The same authors studied dog bile, ox bile, Caroid and sodium taurocholate, with similar results.

Narat and Cipolla [21] investigated the potential of chloroform. They felt that there were several advantages of chloroform over ether: (1) The boiling point of chloroform is 61 C. (141.8 F.) while that of ether is 35 C. (95 F.); (2) the solvent action of chloroform is greater than that of ether; (3) bile pigments are easily soluble in warm chloroform and only slightly soluble in ether, and (4) the solubility factor of chloroform is much greater when the chloroform is warm. They found no demonstrable change in the liver, gall bladder, or biliary ducts of dogs into which they instilled chloroform. It was their conclusion that the use of chloroform was potentially dangerous and should be restricted to the time of surgery. Whipple and Smith [22] were able to diminish bile salt output in dogs by oral administration of small amounts of chloroform. There was no ill effect clinically, normal bile salt output returning in five to seven days. Goldschmidt, Vars, and Ravdin,[23] Miller and Whipple [24] and Whipple and Smith [22] found that protein protected the liver from damage. In the dogs that we killed there was little histologic evidence of liver or ductal damage definitely attributable to chloroform.

In a search for a more effective program, Butsch, McGowan, and Walters,[25] Doubilet and Colp,[26] McGowan, Butsch, and Walters,[27] Bergh,[28] and Best [29] found that glyceryl trinitrate and amyl nitrite promoted sphincter relaxation. The former was found to act more slowly and last longer than the more quickly acting but shorter-lasting amyl nitrite. Doubilet and Colp [26] and Best [29] found that magnesium sulfate relaxed the sphincter but the effect was not too great.

Another approach to the problem of sphincter spasm was through the instillation of topical anesthetics through a T-tube. Glenn and Hill [30] successfully used

20. Strickler, J. H.; Muller, J. J.; Rice, C. O., and Baronofsky, I. D.: Nonoperative Treatment of Retained Postoperative Common Duct Stones, Ann. Surg. **133**:174, 1951.

21. Narat, J. K., and Cipolla, A. F.: Fragmentation and Dissolution of Gallstones by Chloroform, Arch. Surg. **51**:51, 1945.

22. Whipple, G. H., and Smith, H. P.: Bile Salt Metabolism: Liver Injury and Liver Stimulation, J. Biol. Chem. **89**:727, 1930.

23. Goldschmidt, S.; Vars, H. M., and Ravdin, I. S.: The Influence of the Foodstuffs upon the Susceptibility of the Liver to Injury by Chloroform, and the Probable Mechanism of Their Action, J. Clin. Invest. **18**:277, 1939.

24. Miller, L. L., and Whipple, G. H.: Chloroform Liver Injury Increases as Protein Stores Decrease: Studies in Nitrogen Metabolism in These Dogs, Am. J. M. Sc. **199**:204, 1940.

25. Butsch, W. L.; McGowan, J. M., and Walters, W.: Clinical Studies on the Influence of Certain Drugs in Relation to Biliary Pain and to the Variations in Intra-Biliary Pressure, Surg., Gynec. & Obst. **63**:451, 1936.

26. Doubilet, H., and Colp, R.: Resistance of the Sphincter of Oddi in the Human, Surg., Gynec. & Obst. **64**:622, 1937.

27. McGowan, J. M.; Butsch, W. L., and Walters, W.: The Use of Glyceryl Trinitrates (Nitroglycerin) for the Control of Pain Following Cholecystectomy, Ann. Surg. **104**:1013, 1936.

28. Bergh, G. S.: The Sphincter Mechanism of the Common Bile Duct in Human Subjects: Its Reaction to Certain Types of Stimulation, Surgery **11**:299, 1942.

29. Best, R. R.; Hicken, N. F., and Finlayson, A. I.: The Effect of Dehydrocholic Acid upon Biliary Pressure and Its Clinical Application, Ann. Surg. **110**:67, 1939. Best, R. R.[9b]

30. Glenn, W. R., and Hill, W. H.: Common Duct Obstructions Relieved by Injections of a Topical Anesthetic into T Tube, South. Surgeon **14**:3, 1948.

20 cc. of 1 : 500 dibucaine (Nupercaine) hydrochloride and a similar amount of 1.5% piperocaine (Metycaine) hydrochloride. Harris and Marcus [31] employed 1 : 500 or 1 : 1,000 dibucaine hydrochloride with good results.

METHOD OF STUDY

Types of Solutions.—The purpose of this investigation was to study the solvent action of various types of solutions upon gall stones. Table 1 is a classification of these solutions based on their chief chemical characteristics.[32]

Because of the high cholesterol content of the great majority of gall stones, the fat solvents were expected to be quite effective. The surface-tension-lowering agents were studied because of their promise of aiding absorption of the solution

TABLE 1.—*Classification of Solutions*

1. Fat solvents tested
   a. Chloroform
   b. Ether
   c. Ether-alcohol
   d. Alcohol
2. Surface tension lowering agents
   a. Detergent—sorethytan (20) monooleate (N. N. R.); polysorbate (U. S. P.) (Sorlate)
   b. Bile salts
   c. Bile acids
   d. Dog bile and ox bile
3. Calcium-binding agents
   a. Tetrasodium ethelenediaminetetraacetic acid (Versenes)
   b. Citrates
4. Naturally occurring fatty acids
   a. Saturated:
      (1) Caprie (4) Myristic
      (2) Caprylic (5) Palmitic
      (3) Lauric (6) Stearic
   b. Unsaturated:
      (1) Linoleic (3) Oleic
      (2) Linolenic (4) Ricinoleic
   c. Hydroxy fatty acids:
      (1) Ricinoleic
5. Hydrotropic agents
   a. Bile salts
   b. Bile acids
   c. Dog and ox bile
6. Enzymatic agents (hydrolytic)
   a. Trypsin (Tryptar)
   b. Hyaluronidase (Wydase)
   c. Caroid
7. Dispersing agents
   a. Lignin sulfonic compound (Marasperse)
8. Miscellaneous
   a. Strong acids:
      (1) Nitric acid
      (2) Hydrochloric acid
   b. Weak acids:
      (1) Acetic
      (2) Glacial acetic
   c. Boiling water

into the calculus, thus promoting more rapid dissolution. Calcium binding agents were tried because of the varying calcium content of some gall stones. The principle of a chelating agent is that of changing the equilibrium between insoluble calcium salts and calcium ions. This results in removal of the calcium ion, thus converting a hard stone to a soft stone. This type of agent was included because of the known difficulty in breaking up calcium-containing stones. The fatty acids were studied because of the promising effect of lauric acid in preliminary trials. The exact reason for their action was not definitely known. However, it was believed that they might lower surface tension. Enzymes were employed for their possible

31. Harris, F. I., and Marcus, S. A.: Common Duct Stone Relieved by Injections of Nupercaine Solution into T tube, J. A. M. A. **131**:29, 1946.

32. Best, R. R.; Rasmussen, J. A., and Wilson, C. E.: An Evaluation of Solutions for Fragmentation and Dissolution of Gallstones and Their Effect on Liver and Ductal Tissue, Ann. Surg., to be published.

digestant action on the mucous coating of gallstones, thus allowing a more rapid and more effective diffusion of the solvent. Dispersing agents function by absorbing out solid particles and dispersing them by polar action. The miscellaneous group was included for control purposes, as well as to evaluate the possible influence of ionic interchange. Table 2 presents the solutions tested as the basic noncombined agents. Tables 3 and 4 present the various combinations tested with chloroform and ether. A total of 113 different solutions or combinations were investigated.

TABLE 2.—*Solutions Tested Not in Combination*

1. Versenes	1.5%	14. Distilled water	
2. Magnesium citrate	1.0%	15. Nitric acid, dilute	
3. Sodium citrate	5.0%	16. Nitric acid, concentrated	
4. Desoxycholic acid (in alcohol)	1.0%	17. Hydrochloric acid, dilute	
5. Sodium glycocholate	1.0%	18. Hydrochloric acid, concentrated	
6. Sodium taurocholate	1.0%	19. Ethyl ether	
7. Ox bile		20. Chloroform	
8. Dog bile		21. Acetic acid, dilute	
9. Sorlate		22. Aetic acid, glacial	
10. Marasperse C	10.0%	23. Lauric acid (in alcohol)	1.0%
11. Marasperse CB	10.0%	24. Lauric acid (in alcohol)	10.0%
12. Marasperse N	10.0%	25. Lauric acid (in alcohol)	50.0%
13. Ethyl alcohol	95.0%		

TABLE 3.—*Solutions Tested in Combination with Chloroform, Equal Parts*

1. Versenes	1.5%	23. Linoleic acid	1.0%
2. Magnesium citrate	1.0%	24. Linoleic acid	5.0%
3. Sodium citrate	5.0%	25. Myristic acid	1.0%
4. Desoxycholic acid	1.0%	26. Linolenic acid	1.0%
5. Sodium glycocholate	1.0%	27. Oleic acid	1.0%
6. Sodium taurocholate	1.0%	28. Palmitic acid	1.0%
7. Ox bile		29. Ricinoleic acid	1.0%
8. Sorlate		30. Stearic acid	1.0%
9. Marasperse C	10.0%	31. Hyaluronidase (Wydase)	
10. Marasperse CB	10.0%	32. Trypsin (Tryptar)	
11. Marasperse N	10.0%	33. 1% Lauric acid, hyaluronidase (Wydase)	
12. Ethyl alcohol	95.0%	34. 1% Lauric acid, trypsin (Tryptar)	
13. Ethyl ether		35. 1% Caprylic acid, trypsin (Tryptar)	
14. Acetic acid, dilute		36. 1% Linoleic acid, Trypsin (Tryptar)	
15. Acetic acid, glacial		37. Ethyl ether, trypsin (Tryptar)	
16. Lauric acid	1.0%	38. 1% caprylic acid, hyaluronidase (Wydase)	
17. Lauric acid	5.0%	39. 1% Linoleic acid, hyaluronidase (Wydase)	
18. Lauric acid	10.0%	40. Caroid	
19. Lauric acid	50.0%	41. Lauric acid 1%, Caroid	
20. Capric acid	1.0%	42. Caprylic acid 1%, Caroid	
21. Caprylic acid	1.0%	43. Linoleic acid 1%, Caroid	
22. Caprylic acid	5.0%		

Solvent Experiments in Vitro.—In this phase of the problem, dry and fresh gallstones and fresh gallstones with equal parts of common duct bile were immersed in the various solutions. The stones were then observed at periodic intervals up to 48 hours, the initial interval being 15 minutes. All types of gallstones were utilized. The gallstones used in comparable experiments were obtained from the same gall bladder in order to reduce any possible error as a result of variance in composition. The effect was judged by changes in size, shape, and consistency of the gallstones within a given time period. Table 5 lists the solutions which had no demonstrable

effect. The latter solutions in combination with solutions proved to be effective tended to delay or reduce the fragmentation and dissolution action of the useful solvent. The addition of bile and alcohol to the solutions considerably slowed the process of fragmentation and dissolution. The presence of the enzymatic agents occasionally speeded the process. Agitation of the stones in the solution also speeded up the process. When ether and bile are in combination, the stone is suspended in the lower bile layer and the solvent action is negligible without agitation. When

TABLE 4.—*Solutions Tested in Combination with Ethyl Ether, Equal Parts*

1. Versenes	1.5%	24. Lauric acid	1.0%
2. Magnesium citrate	1.0%	25. Lauric acid	5.0%
3. Sodium citrate	5.0%	26. Linolenic acid	1.0%
4. Desoxycholid acid	1.0%	27. Lauric acid	10.0%
5. Sodium glycocholate	1.0%	28. Lauric acid	50.0%
6. Sodium taurocholate	1.0%	29. Stearic acid	1.0%
7. Ox bile		30. Hyaluronidase (Wydase)	
8. Sorlate		31. Ethyl Alcohol, Hyaluronidase (Wydase)	
9. Marasperse C	10.0%	32. Trypsin (Tryptar)	
10. Marasperse CB	10.0%	33. Chloroform, Trypsin (Tryptar)	
11. Marasperse N	10.0%	34. Lauric acid 1%, Trypsin (Tryptar)	
12. Ethyl alcohol	95.0%	35. Linoleic acid 1%, Trypsin (Tryptar)	
13. Ethyl alcohol ⅓ and ethyl ether ⅔		36. Caprylic acid 1%, Trypsin (Tryptar)	
14. Chloroform		37. Lauric acid 1%, Hyaluronidase (Wydase)	
15. Capric acid	1.0%	38. Carprylic acid 1%, Hyaluronidase (Wydase)	
16. Caprylic acid	1.0%	39. Linoleic acid 1%, Hyaluronidase (Wydase)	
17. Caprylic acid	5.0%	40. Ethyl alcohol ⅓, Ethyl ether ⅔, Trypsin (Tryptar)	
18. Linoleic acid	1.0%		
19. Linoleic acid	5.0%	41. Caroid	
20. Myristic acid	1.0%	42. Ethyl alcohol ⅓, Ethyl ether ⅔, Caroid	
21. Oleic acid	1.0%	43. Lauric acid 1%, Caroid	
22. Palmitic acid	1.0%	44. Caprylic acid 1%, Caroid	
23. Ricinoleic acid	1.0%	45. Linoleic acid 1%, Caroid	

TABLE 5.—*Solutions That Did Not Affect Gallstones and Delayed Effective Agents in Their Reactions*

1. Versenes	10. Marasperse C
2. Magnesium citrate	11. Marasperse CB
3. Sodium citrate	12. Marasperse N
4. Desoxycholic acid	13. Ethyl alcohol
5. Sodium glychocholate	14. Distilled water
6. Sodium taurocholate	15. Boiling distilled water
7. Ox bile	16. Nitric acid—dilute or concentrated
8. Dog bile	17. Hydrochloric acid—dilute or concentrated
9. Sorlate	18. Acetic acid—dilute or glacial

chloroform and bile are in combination, the heavier chloroform assumes the lower level and the stone lies in the interphase. Breakdown of the calculus proceeds but can be speeded by agitation.

Chloroform and ether were effective on all stones containing cholesterol. Chloroform was somewhat superior. Mixed stones responded better to chloroform, and in some cases the addition of a fatty acid in a 1% solution to chloroform and ether increased the fragmentation and dissolution. Lauric, caprylic, and linoleic acids were most effective in this regard but were never of sufficient value to justify their use.

Heated chloroform was consistently much more effective than room temperature chloroform. Heating chloroform to near its vaporization point of 61 C. (141.8 F.) produces a significant breakdown of stones within 15 minutes. A comparable effect from room temperature chloroform or ether requires up to 60 minutes. The destruction of fresh stones in warm chloroform is amazingly rapid and complete (Fig. 1). If bile is added, the effect is similar but the rate somewhat reduced.

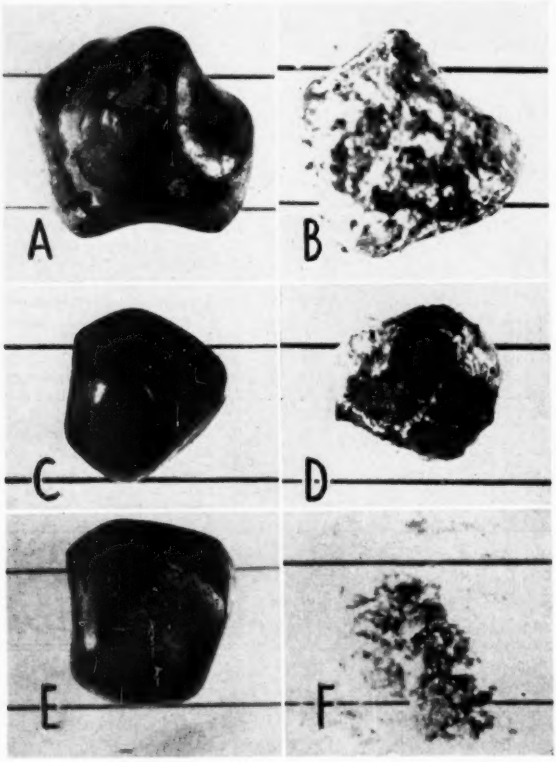

Fig. 1.—*A*, fresh gallstone prior to immersion in ethyl ether. *B*, major dried fragments after 30 minutes' immersion in ethyl ether. Stone about the same size, still rather hard, with cholesterol crystals on its surface. *C*, fresh gallstone prior to immersion in room temperature chloroform. *D*, major dried fragments after 30 minutes' immersion in room temperature chloroform. Note reduction in stone size and some cholesterol crystals on its surface. *E*, fresh gallstone prior to immersion in heated chloroform, 60 C. (140 F.). *F*, major dried fragments after 30 minutes' immersion in heated chloroform. Note complete fragmentation and dissolution because of better solvent effect of heated chloroform on cholesterol and bile pigment. (Scale, 1 cm.)

ANIMAL EXPERIMENTS ON TOXICITY OF CHLOROFORM

For the purpose of evaluating the effect of chloroform on liver and ductal tissue, the drug was instilled into the biliary tract of dogs. After anesthetization with pentobarbital (Nembutal) given intravenously (1 cc. per 2.3 kg. [5 lb. body weight]), the sphincter of Oddi was exposed by a transduodenal approach. A small polyethylene tube was passed through the sphincter up the common duct to the

porta hepatis. The distal end of the tube was brought to the abdominal wall through a small hole in the duodenum, leaving the abdomen via the incision. Chloroform, in 2 to 4 cc. amounts, was injected into the tubing on the third and fourth postoperative days. Prior to instillation, the tubes were opened and bile was permitted to drip for a short time. After instillation, the tubes were clamped to prevent any escape of the drug. Sixteen dogs were used. They weighed between 5 and 22 kg. (11 to 14 lb.). Nine received injections and seven had only the polyethylene tube inserted for control purposes. The animals were killed at intervals from 5 to 30 days. At autopsy, there was minimal gross change in the liver and ductal tissues in both groups, there being no apparent difference. Microscopically there was essentially no injury to the ducts in either group. There was slight to severe liver damage in the form of central lobular necrosis in both groups. This reaction was slightly more consistent in the group which received injections than in the control group. However, some of the dogs which received injections showed minimal liver and ductal changes and had relatively uneventful postinjection courses. Two of the control series died—a mortality of 29%. Four of the dogs which received injections died—a mortality of 44%. In general, the animals given injections recovered more slowly than did those of the control group. At the time of this work, the source of supply of dogs was unavoidably poor. They were, in general, old, poorly nourished, and reluctant to eat well even preoperatively. It should also be noted that the chloroform was a large dose by weight and was always deposited directly into the hepatic ductal system. Comparable instillations in a 70 kg. (150 lb.) man would be 28 to 30 cc. of chloroform.

USE OF CHLOROFORM IN PATIENTS

Ten patients with proved choledocholithiasis were subjected to chloroform instillations. Four to 5 cc. of chloroform heated to 60 C. (140 F.) was injected into the side arm of a double-lumen T-tube on two successive days. Most of the patients complained of some nausea and a little distress, and a few stated the nausea lasted for several hours. Only one patient complained of severe nausea and pain. She was a very nervous, uncooperative patient in whom we questioned using the procedure. She refused to continue with the program after two instillations of chloroform. The remaining patients tolerated the chloroform well and with no ill effects.

COMMENT

The routine use of T-tube drainage following choledochotomy permits early diagnosis of a remaining common duct stone by a choledochogram, gives an advantage for draining or decompressing infected or obstructed biliary ducts, and provides an additional effective mode of therapy. Some surgeons are removing T-tubes without obtaining choledochograms, and some are not using T-tubes but are closing the duct primarily. We cannot understand the rationale behind either omission. It is our opinion that postoperative choledochograms should be obtained for every patient who has undergone exploration of the common duct. If any doubt exists as to the presence of retained stones, the T-tube should be left in place and a repeat x-ray taken. We believe that the frequently demonstrated calculus by postoperative choledochograms is justification for their use, and we see no satisfactory basis for dissent from this opinion. We feel that most stones can be dislodged, and to lose a method of attack is an error.

A new type, wide-angle, double-lumen T-tube to deposit the solution in the distal common duct was reported previously [33] (Fig. 2). This tube has a distinct advantage over others in that it directs the solution away from the liver toward the duodenum and the portion of the common duct where remaining stones are usually seen.

Fig. 2.—This double lumen T-tube has the smaller lumen running along the wider angle to the distal end of the transverse arm of the T-tube. The double lumen end of the transverse arm is directed toward the lower end of the common duct. Solutions injected into the smaller lumen through the side arm will be deposited directly into the region where most remaining common duct stones are located. Tabs have been placed along the longitudinal arm to secure the T-tube to the skin. (Reprinted with permission of Surgery, Gynecology and Obstetrics.[4])

33. Best, R. R.: Choledochostomy—Advantages of a Modified T Tube, Surg., Gynec. & Obst. **90**:295, 1950.

It could also be recommended that the pathology department save all calculi obtained from patients who undergo choledochostomy until satisfactory choledochograms have been obtained. If retained stones were demonstrated, the saved stones could then be tested for solubility in both choloform and ether and the most effective solution or combination employed.

From our investigations we have concluded that chloroform and ether are effective gallstone solvents, room temperature chloroform being somewhat superior and heated chloroform being far superior. If chloroform is used, it should be heated to just under the vaporization point of 61 C. (141.8 F.) and immediately instilled. If ether is used, a patent, nonspastic sphincter is essential, for in our opinion the vaporization pressure of ether (approximately 224 cc. vapor per 1 cc. of liquid either) aids the expulsion of stones lying in the terminal common duct. Care should be used in ether instillations to release the pressure at intervals, as the pain may be intense and there is always the potential of liver cell damage as a result of sustained intraductal pressure. Alcohol has proved to be ineffective and even detrimental if in combination with an effective solvent, such as ether.

We believe that no single method or solution should be used in an attempt to rid the common duct of remaining calculi but, rather, one should use combinations of all the proved methods. It is important to have the patient in as good health as possible and with free bile flow prior to employment of any method. This is to safeguard the liver from any possible toxic effect of drugs used.

The following program is recommended when the postoperative choledochogram, which is usually made on the seventh postoperative day, reveals a remaining common duct stone. The patient is placed on the simplified three-day biliary flush regimen.

1. Three dehydrocholic acid (Decholin) with belladonna tablets after each meal and at bed time for three days.
2. One-half bottle of magnesium citrate (6 oz.) each morning before breakfast.
3. Three tablespoonfulls of pure cream or olive oil before noon and evening meals each day.
4. One glyceryl trinitrate tablet (1/100 grain) dissolved under the tongue before the evening meal each day.

Instillation Technique:

1. By attaching syringe to T-tube, attempt to remove bile from tube and duct.
2. On the first and second days of the biliary flush regimen, heat 4 to 5 cc. of chloroform to 60 C. (140 F.) and instill immediately into the side arm of the double-lumen T-tube.
3. On the third day, slowly instill 5 cc. of ethyl ether into the T-tube, releasing pressure or drawing back on plunger to help control intraductal pressure which gives rise to any distress.
4. Glyceryl trinitrate, 1/100 grain, is given sublingually five minutes prior to the instillation of ethyl ether.
5. A recheck choledochogram is done several days later and if stones are still present the regimen is repeated 7 to 14 days later.

There have been two failures in 14 patients treated. One of these patients had liver stones primarily and both hepatic ducts were packed with stones. After six treatments the last choledochogram finally revealed marked reduction of stones, and we feel encouraged that all stones will ultimately be removed without further operation. The other patient was a very nervous patient who has never completed

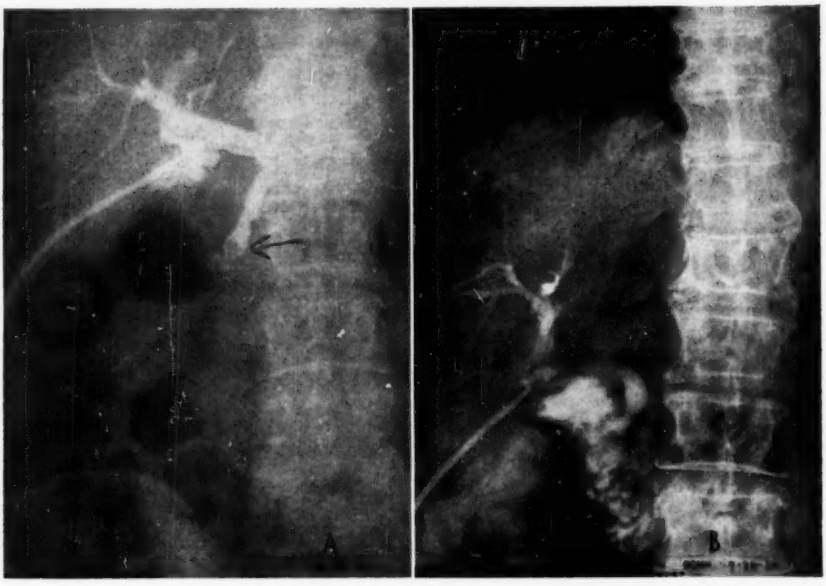

Fig. 3.—*A*, postoperative choledochogram revealing one common duct stone. *B*, choledochogram after two courses of the described regimen, showing a normal biliary tree.

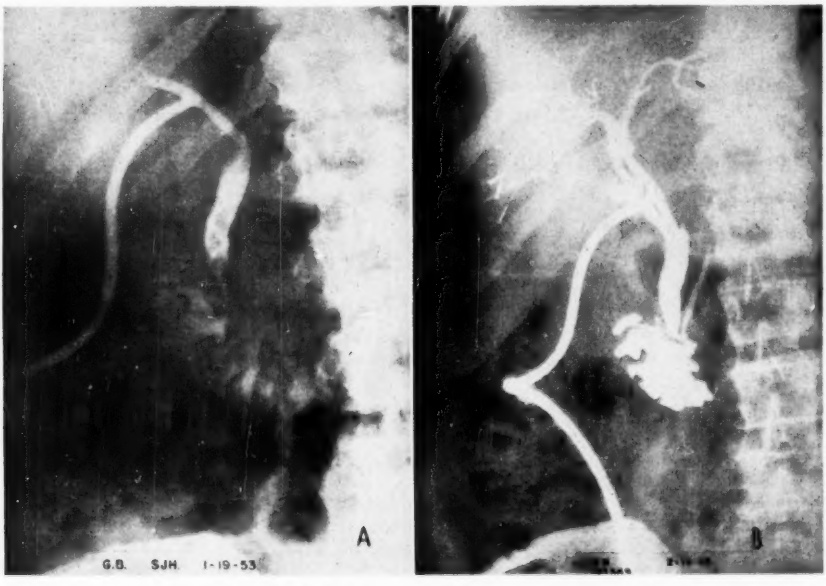

Fig. 4.—*A*, postoperative choledochogram revealing three common duct stones. *B*, choledochogram after one course of the described regimen showing a normal biliary tree.

a full three-day regimen, which makes evaluation difficult. In three patients, success was attained with the first three-day regimen; the others required several courses before the ductal system was free of stones (Figs. 3, 4, and 5). Persistence must be employed because repeated courses of treatment are better than the hazards and difficulties of reoperation, without assurance that all remaining stones will be found or removed.

When a T-tube is placed in the common duct as a splint after stricture repair, it is often left in place for long periods. A difficult problem in this situation is to prevent obstruction of the lumen from encrustations and debris. Not too uncommonly the tube must be removed before ordinarily desired because of complete

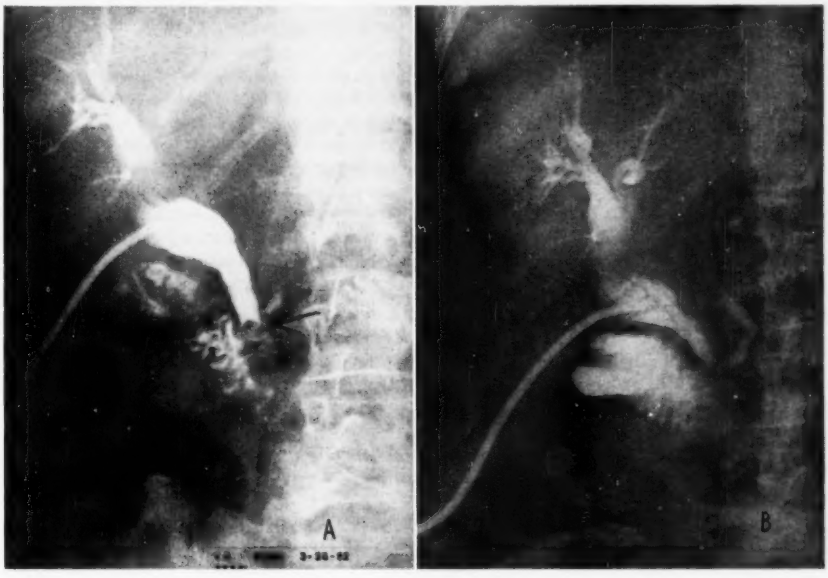

Fig. 5.—*A*, postoperative choledochogram revealing one common duct stone. *B*, choledochogram after one course of the described regimen showing a normal biliary tree.

obstruction, thus jeopardizing the repair. To obviate this complication, it is suggested that the physician instill warm chloroform into the T-tube once a month and that the patient be instructed to take the three-day biliary flush each month.

SUMMARY AND CONCLUSIONS

1. Warm chloroform was the best solvent for gallstones of 113 solutions investigated.

2. No injury of consequence to liver or ductal tissue was demonstrated from use of warm chloroform instillations as described.

3. Chloroform instillations are used on two successive days and ether is used on the third day of the three-day regimen.

4. With the three-day flush regimen, remaining common duct stones revealed by choledochograms were sucessfully removed in only 40% of the cases. The addi-

tion of ethyl ether instillations to the flush regimen resulted in 60% satisfactory results. Now with chloroform and the three-day biliary flush regimen, remaining common duct stones have been successfully dislodged in at least 80% of the cases.

5. Since it is known that stones or debris are frequently present in the common duct when choledochostomy has not been done, the three-day flush regimen is recommended to follow every cholecystectomy. This is usually prescribed about one week postoperatively and is repeated two weeks later. By this method one is able to almost eliminate return of patients with those symptoms presented before their operation.

ABSTRACT OF DISCUSSION

DR. FRANK GLENN, New York: Dr. Best and his group are to be congratulated on going at this problem so wholeheartedly and going through the tremendous number of substances they have in order to find something that would assist in the dissolving of these stones that are overlooked in the common duct.

The problem of overlooked common duct stones is an important one, and those of us who are interested in biliary duct surgery have at times, I think, been chagrined to discover that we have left a stone in the common duct and we have had to go back for it.

My experiences with the old method of trying to dissolve these stones have been so discouraging that I merely want to utter one word of caution in regard to them.

I, like Dr. Walters, I think, have used only ether, I have had that unfortunate experience of using it in patients who had had cholangitis and after the use of the ether solution the patient has had pain, followed by a marked elevation of temperature and a recurrence of jaundice which has been associated with cholangitis and which has been, in my opinion, lighted up.

Now, I think that Dr. Best's contributions are quite as important as the materials they are using and the use of chloroform and ether, but I think that if we are going to use these methods it is extremely important that we follow his instructions very closely in order that the method will be given a fair trial. We intend to do that in our institution.

I should like merely to mention one other aspect of this problem which I believe is of importance—the matter of overlooking stones in the common duct and how it may be prevented.

First of all, I represent the minority, possibly, in this country, in feeling that there are probably far too many common ducts explored. I feel that if there are indications, certainly the common duct should be explored. Now, if it is to be explored, then let us do it with great thoroughness and let us do it carefully and slowly.

I think that haste in common duct explorations is one of the reasons that stones are left behind. I think that very often a stone up in the biliary radicals may come down, if given an opportunity, with the mere flow of bile, to go on at the time of operation.

If we explore a common duct, believing that there are stones there, we will be much more careful than if we explore a common duct and are content to find some granular material, or so-called small stones.

I believe that the use of cholangiograms at the operating table is an excellent practice, but I also am a little discouraged at seeing how carelessly cholangiograms are done, both from the standpoint of the technique employed by the operator and of the radiologists who take these pictures.

Not long ago I was in a hospital in consultation, and a cholangiogram was taken without lowering of the head of the table. As a matter of fact, the head of the table was a little higher than the end, with the result that the biliary tree was not visualized.

I think that we should keep in mind these various steps that may help us not to overlook stones and that we should examine the duct carefully by manual palpation from both sides of the operating table.

We ought to use every bit of ingenuity that we can, and then, I feel, we will partly reach the success that Dr. Walters has.

I think he should be congratulated on having such a remarkable record, and it is one for us all to seek to approach.

I should like to support the contention that the common duct today, if opened, should be drained.

I believe that the practice, which is somewhat on the increase in this country, of closing the common duct without drainage is one that will increase the morbidity from complications and raise the mortality rate, which at present is quite low and which we are eager to get lower.

DR. WALTMAN WALTERS, Rochester, Minn.: For purposes of discussion this study by Drs. Best, Rasmussen, and Wilson can be divided into several parts. The first part is on various solvents of human gallstones. Among the 113 different substances used singly and in combination, Dr. Best and associates have found that warm chloroform and ether have acted best, but sometimes the addition of certain fatty acids and certain of the enzymes has hastened the dissolution of the stones.

The second part of the discussion can center around the use of these substances in the treatment of retained or overlooked stones in the common bile duct. It is gratifying indeed to know of the successful results obtained in 8 of 10 patients from use of a combination of solvents and biliary flushes with relaxation of the sphincter to fragment common bile duct stones and have them passed from the common bile duct. I am sure that use of the new two-way T-tube, which places the very warm chloroform and ether in contact with the stone and with the movements of the patient which agitate the fluid in the duct around the stone, has played an important role in the high percentage of successful results. A third aspect calls for comment on the experimental observations on the effects of warm chloroform instilled into the common bile duct. When the solution of chloroform was brought through a polyethylene tube directly into contact with the finer branches of the bile ducts, especially those within the liver, only slight lobular hepatic inflammation developed and this was of temporary duration. This observation indicates that chloroform can be used in amounts as small as a few cubic centimeters. This seems especially true when the solution could be directed down the ducts, away from the liver to the vicinity of the stone.

Pribram, as the essayists have said, used a catheter to drain the common bile ducts of his patients; he directed the end downward toward the sphincter for a similar purpose rather than upward into the vicinity of the intrahepatic ducts. The T-tube seems more practical to me, since it should give better drainage of bile than the catheter.

I agree with the comments on the value of placing a T-tube in the common bile duct when the common bile duct is opened and explored for stones. I agree not only for the reasons which were mentioned but also because frequently a certain amount of trauma results from the passage of instruments of one sort or another and in my cases of scoops of varying size through the lower end of the common bile duct and the sphincter of Oddi. I am sure that at times this trauma may give rise to some edematous obstruction of this portion of the common bile duct. I have not seen any ill effects from T-tubes placed in the common duct provided that the duct has not been injured when the T-tube was placed in it and provided that a T-tube of a size smaller than the diameter of the duct was used.

The suggestion of using the solvent solutions after operation when a T-tube is to be kept in for any period of time to prevent accumulation of bile sludge, particularly the bile pigment debris, within the lumen of the tube, is, I think, a valuable one, especially if small amounts of the solutions are used.

I have been successful in fragmenting an overlooked stone in the common duct in only the two cases which I reported years ago—but fortunately I have tried to use it in only two other cases, in both of which it was unsuccessful.

The most important aspect of the operation of choledochostomy is, of course, prevention of the surgeon's overlooking a common duct stone. I personally believe that this can be prevented if the surgeon will carefully explore the intrahepatic ducts and the lower end of the common bile duct with scoops. The procedure provides not only for an accurate exploration of the ducts but also for removal of any stones which are present. I believe also that such operations should not be completed until a 4 mm., and whenever possible, an 8 mm., scoop are passed through the lower end of the duct into the duodenum without obstruction and the palpation of the duct over the scoop reveals no other stones to be present. To my knowledge, and I have postoperative cholangiograms in all cases in which I have inserted T-tubes, I have overlooked only three stones in the common bile duct in operations which I have performed since 1945. This I believe is a lower incidence of error than when one depends on cholangiography at the time of choledochostomy.

INTUSSUSCEPTION IN THE ADULT, WITH EMPHASIS ON RETROGRADE TYPE

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SOME UNUSUAL cases of intussusception in adults have been encountered in the past 20 years at Presbyterian Hospital in New York. Since intussusception in the adult produces signs and symptoms differing from those seen in infants, an analysis of 40 cases from the surgical service is presented. All the cases have been well documented by clinical or pathological laboratory findings. Among the patients having exploration were those in whom laparotomy revealed that the invagination had been reduced. In the latter cases x-ray studies diagnostic of intussusception, as well as gross and microscopic pathological findings, were considered sufficient for their inclusion in this study.

INCIDENCE

Intussusception in the adult appears to be an uncommon disorder, a fact which is borne out by a review of the literature. It has been estimated that, of all intussusceptions, the incidence in adults is about 5%.[1] Perrin and Lindsay [2] noted 18 cases of intussusception in persons over 14 years of age among 400 cases of intussusception seen at London Hospital in the 18-year period prior to 1921. Bosworth and Stein [3] cited four cases in 180,266 patients of all types at New York Hospital in the 11-year period preceding 1946, an incidence of 0.003%. The records at Presbyterian Hospital disclosed 40 adult cases among 42,553 ward and semiprivate general surgical patients between January, 1932, and January, 1952, an incidence of 0.094%. In this group 60% were women, although a preponderance of men has been reported by others.[4] Our age incidence reveals half of the patients to be over the sixth decade, at which age there is an increased incidence of cancer (Table 1).

Outstanding reviews of intussusception have been compiled during the past few decades. Freilich and Coe [1a] analyzed 3,284 cases from over 15 reports, including

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1. (*a*) Freilich, E. B., and Coe, G. C.: Jejunal Intussusception, Ann. Surg. **105**:185-191 (Feb.) 1937. (*b*) Iason, A. H.: Intussusception in Adults, Surgery **18**:457-466 (Oct.) 1945.

2. Perrin, W. S., and Lindsay, E. C.: Intussusception: Monograph Based on 400 Cases, Brit. J. Surg. **9**:46-71 (July) 1921.

3. Bosworth, B. M., and Stein, H. D.: Intussusception in Adults: Report of Case Due to Aberrant Pancreas, Am. J. Surg. **74**:801-804 (Dec.) 1947.

4. (*a*) Eliot, E., Jr., and Corcaden, J. A.: Intussusception with Special Reference to Adults, Ann. Surg. **53**:169-222 (Feb.) 1911. (*b*) Freilich and Coe.[1a] (*c*) Perrin and Lindsay.[2]

the excellent articles by Eliot and Corscaden [4a] and Perrin and Lindsay. Other extensive reviews have been presented by Donhauser and Kelly,[5] Goodall,[6] and Brocq and Gueullette.[7] There have been innumerable reports of individual or small series of cases, but, since we make no effort to survey the literature completely, only certain of these will be cited.

MECHANISM AND ETIOLOGY

The term intussusception describes the invagination of one portion of the bowel into a contiguous portion (Fig. 1). An intussusception may gain length, depending on the degree of mobility of the invagination portion and on the relative redundancy and the lack of attachment of the ensheathing bowel. The primary mechanism causing intussusception, as well as the predisposing factors, have been a source of speculative argument for the past 50 years. It has been generally believed that intussusception is induced by an irregular or increased peristalsis resulting from an irritant in the bowel or by a lesion in the wall of the intestine.

In infants, most intussusceptions are ileocecal and ileocolic, and one has seldom found a clear-cut etiological factor. Ferrer,[8] in a comparative review of intussus-

TABLE 1.—*Age Incidence of Intussusception*

Age, Yr.	No. of Cases
Under 20	2
20-29	3
30-39	8
40-49	7
50-59	11
60 and over	9
Total	40

ception in infants and adults at Presbyterian Hospital, suggested as a cause the change of diet at the age of 6 months, in which age group he found the greatest incidence of the condition. He referred also to a theory that lymphoid tissue in the wall of the terminal ileum, particularly abundant in that age group, may be a responsible factor.

In adults a causative factor in the form of a tumor, a Meckel's diverticulum, or other structural abnormalities of the intestinal tract have been reported in the majority of cases. Of the 40 cases in our series, 26 (65%) had a demonstrable organic cause. Of these, tumors of the intestinal wall were encountered in 24 patients. The tumor, in most cases forming the apex of the invaginating segment, was malignant in 16 cases and benign in 8 (Table 2). On the other hand, Eliot and

5. Donhauser, J. L., and Kelly, E. C.: Intussusception in the Adults, Am. J. Surg. **79**:673-677 (May) 1950.

6. Goodall, H. W.: Chronic Primary Intussusception in the Adult, Boston M. & S. J. **162**:448-452 (April 7) 1910.

7. Brocq, P., and Gueullette, R.: L'invagination intestinale de l'adulte: Formes cliniques et étude radiologique, J. chir. **28**:369-392 (Oct.) 1926.

8. Ferrer, J. M., Jr.: Symposium on Surgical Emergencies: Intussusception in Children and Adults; Critical Review with Addition of 38 New Cases, S. Clin. North America **30**:515-528 (April) 1950.

Corscaden [4a] noted that in 60% of their patients with tumors the lesion was benign. Perrin and Lindsay [2] noted that 28% of 400 intussusceptions had been caused by tumors. The many case reports in the literature have revealed a variety of tumors producing intussusception. Among the benign types have been lipoma,[9] adenoma,[10] polyp,[11] and neurofibroma.[12] The malignant lesions have been largely adeno-

Fig. 1.—Intussusception of cecum (gangrenous tip) and ascending colon into transverse colon of 46-year-old man. Perforation of transverse colon (*arrow*) had been occluded by head of intussusception. No tumor or other specific etiological agent was found. (Copy from color transparency.)

TABLE 2.—*Incidence of Tumors in Large and Small Bowel*

Tumor	Large Bowel	Small Bowel
Carcinoma	8	2
Lipoma	3	1
Lymphosarcoma	..	5
Fibroma	..	2
Leiomyoma	..	1
Polyp	..	1
Malignant melanoma (metastatic)	..	1
Total	11	13

9. (*a*) Sussman, M. L.: The Roentgenologic Aspect of Subacute and Chronic Intestinal Intussusception, Am. J. Roentgenol. **27**:373-382 (March) 1932. (*b*) Massachusetts General Hospital Case 34492, New England J. Med. **239**:897-898 (Dec. 2) 1948. (*c*) Granusman, R. I., and Rogers, S. S.: Surgery of Ileal Tumors: Report of a Case of Intussusception Led by Lipoma of the Ileum, Am. J. Surg. **77**:387-391 (March) 1949. (*d*) Botsford, T. W., and Newton, F. C.: Intussusception in an Adult due to Submucous Lipoma of the Ileum, Surgery **10**:265-269 (Aug.) 1941.

10. (*a*) Christopher, F.: Intussusception in Adults: Two Additional Cases, Surg., Gynec. & Obst. **63**:670-674 (Nov.) 1936. (*b*) Williams, C., and Williams C., Jr.: Intussusception due to Familial Adenoma of Small Intestine, Arch. Surg. **59**:250-257 (Aug.) 1949. (*c*) Iason, A. H., and Filberbaum, M. B.: Intussusception in an Adult Associated with Adenoma of the Ileum, Ann. Surg. **93**:1191-1196 (June) 1931.

11. Groper, M. J.: Retrograde Enteric Intussusception, Ann. Surg. **112**:344-351 (Sept.) 1940. Sussman.[9a]

12. Atkinson, A. J.; Wheelock, M. C., and Teloh, H. A.: Case Report of Neurofibroma of Jejunum with Intussusception, Gastroenterology **13**:351-356 (Oct.) 1949.

carcinoma [13] or occasional sarcoma.[13b] Both small intestine and colon have been involved by these growths. Cases have been reported in which the tissue was ectopic pancreas [14] or endometrium.[15]

The other two cases in our series with a proved organic basis had a diverticulum of the cecum and a very mobile cecum because of an abnormal mesentery as the causative factors. In the two cases small intestine and some part of the cecum formed the head of the intussusception. It is interesting that a Meckel's diverticulum was not encountered in our series, although this lesion has been considered second in incidence to tumor as a causative agent. Drummond [16] analyzed 78 cases of Meckel's diverticulum and noted 6.4% associated with intussusception. Many subsequent reports have implicated Meckel's diverticulum as a cause of intussusception.[17]

While some authors have stated that intussusception is always secondary to some underlying cause,[10b] others have supported the possibility of there being a familial tendency toward intussusception.[18] The occurrence of intussusception on a reflex basis is suggested by certain reports in which an invagination followed aortography and use of autonomic [19] drugs or was associated with acute trauma, inflammation of the bowel, or mesenteric [20] lymph nodes.

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13. (*a*) Massachusetts General Hospital Case 35122, New England J. Med. **240**:476-477 (March 24) 1949. (*b*) Good, C. A.: Entero-Enteric Intussusception, Radiology **42**:122-127 (Feb.) 1944. (*c*) Black, B. M.: Polypoid Carcinoma of the Ileum Producing Intussusception: Primary Resection with Recovery of Patient, Proc. Staff Meet., Mayo Clin. **19**:142-146 (March 22) 1944. (*d*) Wardill, W. E. M.: Polypi in the Bowel Causing Intussusception, Brit. J. Surg. **13**:158-162 (July) 1925. (*e*) Thorek, P., and Lorimer, W. S., Jr.: Retrograde Intussusception, J. A. M. A. **133**:21-23 (Jan. 4) 1947.

14. Ripstein, C. B.: Intussusception due to Heterotopic Pancreas: Report of a Case, Surgery **25**:76-77 (Jan.) 1949.

15. Southern, E. M.: Aberrant Endometrical Tissue and Intussusception, Brit. M. J. **1**:1178-1180 (June 19) 1948.

16. Drummond, H.: Inversion of Meckel's Diverticulum: With a Report of 6 Cases, Ann. Surg. **55**:404-415 (March) 1912.

17. Martin, J. D., Jr., and Dennis, E. W.: Intussusception: A Comparison of the Infant and Adult Types, South. Surgeon **16**:527-536 (June) 1950. Greenfield, J., and Smoak, P. L.: Intussusception due to Invaginated Meckel's Diverticulum in Adults, ibid. **15**:505-511 (July) 1949. Wasmann, R.: Über Darminvagination bei Erwachsenen, Chirurg **21**:642-644 (Nov.) 1950. Gadbois, R. W.; Dean, M. A., and Johnson, W. E.: Treatment of Intussusception Caused by Invaginated Meckel's Diverticulum: Report of Case, with Review of Experience in Community Hospital, New England J. Med. **241**:595-600 (Oct. 20) 1949. Campbell, R. E.; Churney, O. L., and Botsford, T. W.: Recurrent Intussusception Caused by Meckel's Diverticulum, Bull. U. S. Army M. Dept. **9**:750-754 (Sept.) 1949. Christopher.[10a] Footnote 13*a*.

18. Hipsley, P. L.: Intussusception, Brit. M. J. **2**:717-721 (Oct. 19) 1935. De Cesare, N. F.: Enteric Intussusception in the Adult, Am. J. Surg. **77**:532-536 (April) 1949.

19. Courty, A., and Carli, G.: Invagination intestinale aigue après aortographie: Essai d'interprétation; Déductions pratiques, Gaz. méd. françe **57**:719-722 (Aug.) 1950.

20. Falor, W. H.: Multiple Intussusceptions, Direct and Retrograde, of Traumatic Origin, Ann. Surg. **127**:730-737 (April) 1948. Umiker, W.: Fatal Viral Hepatitis Complicated by Phlegmonous Cecitis and Ileocecal Intussusception, Arch. Path. **46**:493-497 (Nov.) 1948. Marr, N. G., and Marxer, O. A.: Intussusception of the Jejunum, Lancet **2**:392-393 (Aug. 20) 1932. Goodall, H. W.: Chronic Primary Intussusception in the Adult, Boston M. & S. J. **162**:491-499 (April 14) 1910.) Goodall.[6]

One cannot deny that there have been cases in which the underlying cause has been diligently sought but never demonstrated.[21] In our own series of cases there were 10 (25%) in which no demonstrable organic basis for the intussusception could be found. Of these, seven had evidence of recent intussusception at the time of operation, but it had been reduced either spontaneously or as the result of a barium enema. The preoperative diagnosis of intussusception was supported by the clinical findings and x-ray studies. Of the remaining cases, in one an intussusception was found at operation and reduced by the surgeon, and in two surgery was not required, the patients having remained free of symptoms after reduction of the intussusception, presumably by barium enema. In none of these 10 cases did the diagnostic studies, surgical exploration, or examination of resected bowel demonstrate an organic lesion.

In five of our cases (12.5%) there was evidence that the intussusception was caused by the presence or withdrawal of a Miller-Abbott tube from the small bowel. Intussusception resulting from tubes has been reported by others.[22]

The classification of our cases by type reveals that, of the total number, 33 (92%) were cases of simple intussusception. Three (8%) were compound, i. e., an

TABLE 3.—*Areas of Intestine Involved in Intussusception*

Intussusception	No. of Cases
Ileocecal	8
Cecocolic	6
Jejeunojejeunal	6
Ileoileal	6
Colocolic	5
Ileocolic	4
Sigmoidorectal	3
Sigmoidosigmoid	1
Ileoileosigmoid	1
Total	40

intussusception was found to have passed en masse into a contiguous portion. Thirty-one (86%) were isoperistaltic; whereas five (14%) were retrograde in direction. This type has been an uncommon variety, except for those associated with retrograde prolapse of jejunum through the stoma of a gastroenterostomy. We have excluded this particular group from our consideration, limiting our discussion to intussusception which involves only the intestine. The areas of bowel which were involved in the intussusceptions in our cases are indicated in Table 3.

SIGNS AND SYMPTOMS

The symptoms in adult intussusception are varied, yet several signs and symptoms occur often enough to merit attention. Cramping abdominal pain occurred in a great majority of the patients (75%) prior to treatment. Of those patients, 75%

21. Ryan, T. F. J., and Morgan, J. W. P.: Acute Primary Intussusception of the Jejunum, Brit. M. J. **1**:613-614 (March 25) 1939. Hanson, P. B.: Om spontane kroniske tarminvaginationer hos voksne, Ugesk. læger **108**:1047-1052 (Sept.) 1946. Williams, S. H., Jr.: Acute Primary Ileo-Ileal Intussusception in an Adult: Report of a Case, North Carolina M. J. **8**:776 (Dec.) 1947. Freilich and Coe.[1a] Brocq and Gueullette.[7]

22. (*a*) Nichols, H. M.: Intussusception Occurring After Intubation of Small Intestine: Report of Case, Northwest Med. **45**:924-925 (Dec.) 1946. (*b*) Dunn, D. D., and Shearburn, E. W.: Jejunal Intussusception: Unusual Complication of Use of Miller-Abbott Tube, Surgery **26**:833-836 (Nov.) 1949.

showed radiation of pain from the point of origin. Nausea and vomiting were the next most common complaints and occurred in 68% of the patients. Disturbance of bowel function proved to be an unreliable guide in diagnosis. In 34 patients in which bowel activity was noted to be affected, 15 had constipation, whereas 10 had diarrhea. Function was reported as being normal in five patients and irregular in four. Abdominal distention was present in 45%, a palpable abdominal mass in 55%, and abdominal tenderness in 60% of the patients.

Fig. 2.—Roentgenogram obtained at 30 minutes during a small intestinal series reveals a jejunal intussusception in an adult. At the level of the third lumbar vertebra there is noted a marked narrowing of the longitudinal mucosal pattern, as well as a local widening of the bowel with the usual semicircular mucosal markings. (Courtesy of Dr. Ross Golden, Department of Radiology.)

Gross blood was present in the stools in only 42% of the cases in which this factor was recorded. The guaiac test for occult blood contributed little to the establishment of a diagnosis, the test being recorded as positive only in those cases in which gross blood was present in the stools. A notable feature was the absence of pyrexia in our patients, except three in which the rectal temperature was only slightly above 100 F.

Laboratory findings, with the exception of the x-ray, contributed little to the diagnosis. A white blood cell count greater than 15,000 was recorded in only five instances. Interestingly, of the five cases in which there was gangrenous bowel, only one patient had a leucocyte count above 10,000 cells per cubic millimeter.

Survey roentgenograms of the abdomen were of diagnostic value in few of the cases. However, absence of a cecal shadow in the right lower quadrant in several cases of ileocolic intussusception may have given a clue to the diagnosis preoperatively. Barium studies, represented by either gastrointestinal series or barium enema, were diagnostic in only 19 (70%) of the 27 cases in which these tests were used. Many excellent reviews have appeared outlining the roentgenographic aspects of experimental and clinical intussusception. Among them, Brocq and Gueullette,[7] Sussman,[9a] and Good [13b] have integrated the clinical and roentgenographic features essential to the diagnosis of intussusception. They are (*a*) obstruction to the free passage of barium, (*b*) gradual narrowing of the lumen proximal to the lesion, (*c*) marked narrowing of the longitudinal mucosal pattern at the site, (*d*) a local widening of the bowel with the usual semicircular mucosal markings (concentric ring or spiral sheath), (*e*) palpable mass at site, and (*f*) change in position and shape following defecation. Certain of these features are shown in one of our patients (Fig. 2).

REVERSE INTUSSUSCEPTION

This form of intussusception is uncommon and deserves special mention. One of the earliest reported series of this type was that of Fitzwilliams [23] in 1908, in which six cases of the retrograde type were found in a series of 1,000. Nichols,[22a] in 1946, reported a case in which the balloon of a Harris tube became caught at the site of an intestinal anastomosis, resulting in a reverse ileoileal intussusception upon attempted withdrawal.

The following are summaries of five cases of the reverse type of intussusception, the etiology of which was apparently associated in four cases with the presence or withdrawal of a Miller-Abbott tube.

CASE 1.—D. P., a 54-year-old Negro woman, had a history of a pregnancy 20 years before her most recent admission to the hospital, but the patient had never gone into labor and had never been delivered of a child. The diagnosis of abdominal pregnancy and lithopedion had been made, but the patient had refused operation. She was followed in the outpatient clinic, where it soon became apparent by barium studies that she had an ileosigmoidal fistula. Operation was refused until seven years later, at which time she was admitted with a history of five weeks of nausea and vomiting and increased lower abdominal pain over a 24-hour period. Proctoscopic examination then revealed an gangrenous mass of intussuscepted bowel in the rectum. Laparotomy revealed the ileosigmoidal fistula. In this region a mass of adhesions had produced torsion of the bowel and a reverse ileoileal intussusception. The intussusceptum had passed backwards through the fistula into the sigmoid colon and rectum. The invagination was reduced, and a segment of gangrenous ileum was resected. The postoperative course was uneventful. However, two years later studies disclosed multiple fistulae had developed between large and small bowel. Multiple polyposis of the rectum and sigmoid colon was noted as well. Laparotomy was again carried out, with closure of the fistulae, multiple enteroenterostomies, and appendectomy. The patient has subsequently been well over a 12-year follow-up period.

CASE 2.—K. W., a 44-year-old Negro woman, was admitted to the hospital complaining of cramping lower abdominal pain, nausea, and vomiting of 24 hours' duration. The patient had undergone hysterectomy five years previously, with subsequent sound disruption and paralytic ileus. The severity of nausea, vomiting, and mild distention prompted the insertion of a Miller-Abbott tube, which satisfactorily traversed the small intestine, with complete relief of the patient's symptoms. On the fourth day of hospitalization, withdrawal of the tube 2¼ ft. (76.20 cm.) resulted in severe right lower quadrant pain. Barium instilled in the tube revealed the tip

23. Fitzwilliams, D. C. L.: The Pathology and Etiology of Intussusception from the Study of 1,000 Cases, Lancet **1**:628-633 (Feb. 29) 1908.

to be in the proximal ascending colon and showed the presence of a reverse colocolic intussusception in the area. The balloon of the tube was accordingly reinflated and the tube allowed to pass through the rectum. Repeated roentgenograms showed no evidence of intussusception, and the patient was discharged on the following day, free of symptoms.

CASE 3.—H. F., a 54-year-old white woman, was admitted with a 24-hour history of cramping lower abdominal pain. It had sudden onset in the right lower quadrant, accompanied by nausea and repeated vomiting. The only previous surgery had been a cervical dilation and curettage, with repair of a lacerated cervix four years prior to admission. Physical examination revealed a thin dehydrated woman who had slight abdominal distention and moderate tenderness in the right lower quadrant. Peristaltic signs were absent. There was some rectal tenderness high on the right side. Surgical exploration revealed a congenital failure of fusion of the entire colon to the posterior abdominal wall. A loose torsion of the colon had occurred in such a manner that the appendix lay in the left upper quadrant. The torsion was corrected, and appendectomy was performed. Postoperatively the moderate signs of obstruction and distention required the insertion of a Miller-Abbott tube on the third day. It was removed 10 days later, but, after a week, distention once more necessitated its replacement. Because of persistent mechanical ileus, laparotomy was again performed. An internal strangulated herniation of ileum had occurred into a pelvic pocket formed by loops of bowel, adhesions, and a hiatus in the left bowel ligament. The Miller-Abbott tube had advanced to within 1 ft. (30.48 cm.) of this area. The portion of the bowel in which the tip lay, although decompressed, was intussuscepted not only forward but also backward upon the tube and itself in several places. In this case the intussuscepted portion was easily reduced, but the presence of a gangrenous loop of bowel at the site of herniation made resection necessary. Accordingly, partial iliectomy and ileoileostomy were performed, following which the patient made an uneventful recovery.

CASE 4.—A. B., a 36-year-old Negro woman, was admitted to the hospital with a four-year history of progressive abdominal pain, mostly in the right lower quadrant. The pain, which previously had been intermittent in type, was reported to have been more constant during the three months prior to admission. An exploratory laparotomy revealed nothing to account for her symptoms, but prophylactic appendectomy was performed. Postoperatively the Miller-Abbott tube, which had been inserted in preparation for a possible ileocolectomy, was removed. During the subsequent seven days, increasing nausea, vomiting, and distention recurred. Reoperation disclosed a reverse intussusception with distal ileum invaginated into proximal ileum for a distance of 15 cm. This was considered to be caused by withdrawal of the Miller-Abbott tube. A small partial wound disruption at the site of the previous operation was discovered also and was repaired. Postoperatively there was a transient mild ileus, and infection of the two wounds developed. The patient recovered but later needed excision of a superficial sinus of the abdominal wall.

CASE 5.—W. W., a 50-year-old Negro woman, was transferred from the Medical Service with signs and symptoms of mild intestinal obstruction. She was being treated for a recent myocardial infarction and cardiac decompensation and had had cholecystectomy with drainage, six months previously. When the patient was transferred to the Surgical Service, a Miller-Abbott tube was inserted with fluoroscopic control into the duodenum; with the balloon inflated, the progress of the tube was rapid for about an hour and one-half. The patient then complained of a pulling sensation in the abdomen and stated that the tube felt tight. Half an hour later she was seized with sudden, very severe, constant lower abdominal pain and displayed symptoms of shock. A diagnosis of perforated viscus was made. Supportive measures were instituted and a laparotomy performed. At operation an intertwined mass of ileal loops with peritoneal adhesions was found in the vicinity of the old operative scar. Distally the ileum was normal to the ileocecal valve, but proximally the bowel was taut. There was a perforation of the ileal wall at a site where the adherent loops were attached by adhesions to the abdominal wall at the old scar. The tip of the Miller-Abbott tube was proximal to the mass, and a retrograde ileoileal intussusception had occurred 1 ft. (30.5 cm.) proximal to the tip of the Miller-Abbott tube. It seemed conceivable that the ileum had invaginated backwards upon itself and the Miller-Abbott tube with force sufficient to tear the ileum at its point of fixation to the old scar. The tube had not been fixed in position to the nose. Postoperatively the patient's condition deteriorated rapidly, and, in spite of all supportive measures, she died 48 hours later.

Four of the above cases, all of which occurred within the past five years, are significant primarily because of their common etiology. Smith,[24] in 1945, wrote concerning the use of Miller-Abbott tubes in this hospital and made no mention of retrograde intussusception up to that time. In each of the cases presented here, it seemed indisputable that the presence of a Miller-Abbott tube or its sudden withdrawal was responsible for the reverse intussusception. A complete understanding of predisposing factors, however, is less possible, and drawing conclusions from a series of four cases would appear presumptuous. Nevertheless, there are one or two facts which we consider to be of interest. All four patients were women who had undergone some form of abdominal or pelvic surgery. In two cases the presence of fixed matted loops of bowel a short distance from the end of the Miller-Abbott tube appeared to be associated with the formation of the reverse

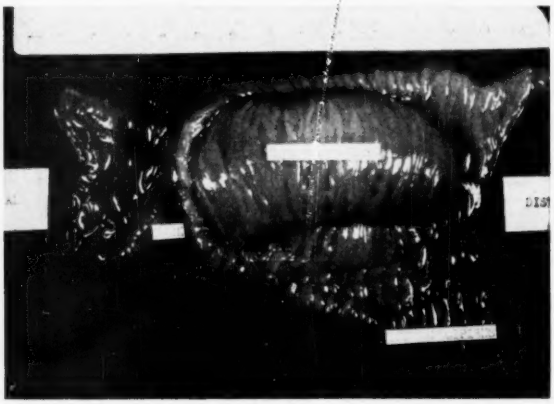

Fig. 3 (Case 6).—Intussusception in upper jejunum. The neck is marked by the small white tab. The intussusception, or invaginated segment, is marked by the upper long tab, and the intussuscipiens is marked by the lower long tab. The lesion appeared to be related to the use of a Miller-Abbott tube. (Copy from color transparency.)

intussusception. In two cases the relatively rapid withdrawal of long segments of the Miller-Abbott, tube, which had progressed far down the intestine, was considered to have caused the disorder. This experience would suggest that such tubes should be removed slowly in stages.

After introduction of the tip of a Miller-Abbott tube into the stomach, 2 cu. cm. of mercury have been introduced into the balloon to facilitate passage of the tip through the pylorus. The balloon has then been inflated and the tube allowed to progress as usual. Whether or not the mercury within the balloon constitutes an added precipitating factor in the formation of intussusception is difficult to say. The reverse intussusception reported by Nichols [22a] was due to the use of a Harris tube containing mercury in the balloon.

Another possible contributing factor is the duration of intubation. It seems conceivable that prolonged intubation might allow for more "accordion effect," the bowel loops folding themselves tightly upon and "climbing up" the immobile tube.

24. Smith, B. C.: Experiences with the Miller-Abbott Tube: Statistical Study of 1,000 Cases, Ann. Surg. **122**:253-259 (Aug.) 1945.

An additional instance of intussusception in which the presence or rapid withdrawal of a Miller-Abbott tube seems associated is presented.

CASE 6.—P. J., a 47-year-old Negro woman, was admitted to the hospital with cramping abdominal pain of two days' duration. She had had a panhysterectomy four years previously, and this history, together with x-ray findings at admission, suggested a diagnosis of intestinal obstruction on the basis of postoperative adhesions. At laparotomy, a cicatrizing carcinoma of the ascending colon was found, and partial ileocolectomy with transverse ileocolostomy was performed. No other pathology was found at operation. Postoperatively the passage of a Miller-Abbott tube was attended by technical difficulty, requiring considerable manipulation of the tube. During a few days the Miller-Abbott tube was alternately partially withdrawn and allowed to progress and eventually was removed entirely. The patient then displayed signs and symptoms of high obstruction of the small bowel. The tube was reintroduced but could not be passed beyond the ligament of Treitz. Instillation of barium revealed evidence of an intussusception of the upper jejunum. A second laparotomy was performed 21 days after the first operation. A jejunojejunal intussusception 10 cm. in length was found 15 cm. distal to the ligament of Treitz (Fig. 3). The intussuscepted portion was resected, and a jejunojejunostomy was done. During the resection an interesting additional lesion was revealed on digital examination within the lumen of the duodenum just proximal to the ligament of Treitz. Here, an annular constricting band, probably congenital in origin, narrowed the duodenal lumen to fingertip size. Persistent duodenal distention, presumably because of this, made necessary a gastrojejunostomy. The postoperative course was uneventful. Recurrence of carcinoma two years later led to her eventual death.

TABLE 4.—*Types of Surgery Employed for Intussusception*

Type of Operation	No. of Cases
Segmental resection of intussusception	26
Reduction with local excision of tumor	4
Repair of perforated bowel	1
Repair of wound dehiscence	1
Laparotomy	3
Laparotomy and cecopexy	1
Total	36

TREATMENT OF INTUSSUSCEPTION

Among the group of cases presented here, no operation was performed in four cases. Two of these were cases of recurrent intussusception of the transverse colon which were reduced by barium enema; the patients were discharged from the hospital symptom-free, having refused exploration. In another case a sigmoidorectal intussusception on the basis of a carcinoma of the sigmoid colon was not suspected clinically. A cecostomy was performed to relieve large bowel distention, but the patient died of peritonitis and inanition. Only at postmortem examination was a gangrenous intussusception recognized.

In the remaining 36 cases various types of operative intervention were employed (Table 4). At laparotomy the intussusception was found already reduced in three cases. In two cases no definitive procedure was needed, but in the other case cecopexy was performed.

Simple reduction of the intussusception was accomplished in five cases. In three of these, excision of the causative benign tumor was carried out. Definitive resection of the intussuscepted segment was performed in the remaining 26 patients. In one of these, ileocolostomy was carried out after removal of the causative malignant tumor.

It has been noted that effective treatment should include early and adequate surgery. Interestingly enough, the first operation performed for intussusception, by Bonetus in 1700, was performed on an adult woman. The second operation, on a 50-year-old woman, was reported in 1751 by Velse. Our experience at Presbyterian Hospital supports this implication that operation is indicated more frequently in the adult than in infants.[8] Morbidity and mortality will vary according to underlying cause, site, and duration of the intussusception and effectiveness of supportive measures before exploration.

Since many of the intussusceptions in adults involved the small bowel, preoperative management may involve replacement of serious loss in fluid and electrolytes. Such readjustment warrants a delay in operation, since proper preparation will inevitably reduce surgical mortality in such cases.

SUMMARY

An analysis of 40 cases of adult intussusception has been presented. Histories of five unusual cases of reverse intussusception, four of which were believed caused by the presence or sudden withdrawal of a Miller-Abbott tube, have been presented. The other reverse intussusception occurred through an enterocolic fistula secondary to the presence of an abdominal lithopedion. An additional case of isoperistaltic intussusception of the proximal jejunum, also believed attributable to the Miller-Abbott tube, has been presented.

ACUTE ARTERIAL EMBOLISM

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EMBOLIC disease is not an uncommon entity. It is, perhaps, a poorly understood emergency, as may be witnessed by its delayed recognition and by its varied and even harmful treatment, both by the general surgeon and by the general practitioner. The present study is comprised of a survey of 85 patients admitted to the University Hospitals over an 18-year period from 1934 to 1952, whose conditions were diagnosed as visceral or peripheral embolic disease. Patients with embolism primarily to the brain, heart, and lungs were excluded. The recent advances in cardiac and peripheral vascular surgery offer encouraging aspects to the treatment of this condition and necessitate a more complete evaluation of its basic clinicopathology.

INCIDENCE

Of the 85 patients admitted during an 18-year period, there was only a slightly higher incidence in women. Thirty-eight of the patients were men and 47 were

TABLE 1.—*Incidence of Peripheral Arterial Embolism by Decades*

Age, yr.	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90
Patients, no.	0	1	3	15	23	28	13	2

women. The average age was 60 years; the youngest patient was 27 and the oldest, 85. A study of Table 1 shows the peak incidence (60%) to be within the fifth and sixth decade. Of all the patients, 90% were between the fourth and seventh decades.

ETIOLOGICAL DISEASE

The embolism may be assumed to arise from the heart in almost all cases. The primary cardiac disease incidence in this series may be ascertained from Table 2. Of the cases, 52 (61%) were classified as arteriosclerotic and/or hypertensive cardiovascular disease. The incidence of infarction and formation of mural thrombus was high in this group, as was confirmed clinically by electrocardiography or by autopsy. Ventricular aneurysm, aortic aneurysm, and aortic thrombi secondary to arteriosclerosis were found as other sources of emboli in this group. Rheumatic heart disease comprised 28 (33%) of the cases, 2 of which were complicated by

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subacute bacterial endocarditis. The formation of vegetations secondary to rheumatic valvulitis and endocarditis is adequate explanation for a source of embolism. One case of hyperthyroidism and auricular fibrillation, one of congenital heart disease, and three of bronchopneumonia comprise the remaining primary diseases. All pneumonia cases were the bronchopneumonia type of virus etiology. In one of these cases the patient was described as having a toxic myocarditis.

The association between embolism and primary cardiac disease appears to have a common denominator in auricular fibrillation. This arrhythmia is commonly accompanied by the formation of thrombi either of the wall of the auricle or in the auricular appendage. Twenty-seven of 28 patients with rheumatic heart disease with embolism had auricular fibrillation. The remaining patient with rheumatic heart disease had subacute bacterial endocarditis, and the valvular vegetations presumably were the source of the embolus. Thirty-nine patients with arteriosclerotic heart disease had auricular fibrillation, 12 had normal sinus rhythm, and 1 had a complete auriculoventricular block. Ten of the 12 with normal rhythm had previous

TABLE 2.—*Summary of Associated Diseases with 106 Acute Emboli in 85 Patients*

	Patients, No.	Average Age, Yr.	Patients with Fibrillation, No.	Cardiac Disturbance Present	Total No. Embolic Episodes	Acute Episodes	Confirmation			Results *			
							Clinical	Operation	Autopsy	1	2	3	4
Rheumatic	28	49	27	28	58	34	19	10	5	8	5	5	21
Arteriosclerotic	52	66	39	50	87	66	30	16	20	23	11	3	17
Bronchopneumonia	3	53	1	1	3	3	2	1	0	0	1	0	2
Hyperthyroid	1	62	1	1	2	2	1	1	0	1	0	0	2
Congenital	1	27	0	1	1	1	1	0	0	0	0	0	1
Total	85	60	68 (80%)	81 (95%)	151	106	53	28	25	31	17	8	48

* Results are indicated according to Haimovici's classification (See text).

myocardial infarcts with probable mural or aneurysmal thrombi. One patient with bronchopneumonia and toxic myocarditis and the one patient with hyperthyroidism had fibrillation. Two patients with bronchopneumonia and one with congenital heart disease had normal sinus rhythm. The tendency for congenital hearts to form intracardiac thrombi is well established. In 95% of the cases presented therefore a known pathological or functional cardiac disturbance was present. In Haimovici's [1] series of 228 patients, the heart was the source of embolism in 96%. Warren and Linton [2] reported on 88.7% with cardiac disease.

Most of our patients were under medical treatment prior to their embolic episode. Because auricular fibrillation is such a prominent feature in these cases, the question of conversion to normal rhythm is frequently proposed, even though the arrhythmia is chronic in nature. Two of our cases suggest that conversion to normal sinus rhythm precipitated the embolic episode. Warren and Linton in a study of 98 patients with 172 emboli did not observe any such sequence of events.

1. Haimovici, H.: Peripheral Arterial Embolism: A Study of 330 Unselected Cases of Embolism of the Extremities, Angiology **1**:20-45, 1950.

2. Warren, R., and Linton, R. R.: The Treatment of Arterial Embolism, New England J. Med. **238**:421-429, 1948.

Table 2 correlates the etiological disease with the prognosis. A total of 106 acute embolic episodes in the 85 patients were studied. Approximately one-half of these were confirmed by autopsy or by operation. The remainder were diagnosed by clinical methods. The results are classified according to the system of Haimovici [1] as follows: Class 1, ischemia followed by early death; Class 2, ischemia followed by necrosis; Class 3, ischemia followed by chronic ischemia, and Class 4, ischemia followed by anischemia.

The rheumatic group, with patients of the youngest average age, had an average of two embolic episodes per patient. In 21% of this group, acute emboli contributed to the cause of death, and in another 13% necrosis resulted. Approximately 54% survived without symptoms, whereas the remaining 13% had chronic ischemia. The arteriosclerotic patients averaged slightly less than one and one-half embolic episodes per patient. The mortality factor in the group was 41%. Necrosis resulted in 21%, while 6% had symptoms of ischemia. The survival rate without symptoms was 32%. In one of the patients with bronchopneumonia, necrosis developed, and the hyperthyroid patient had two emboli, one to the superior mesenteric artery which was fatal.

From these figures we conclude that in patients in the younger age group and in those with rheumatic disease the survival rate is better and necrosis is less likely to develop, but there is a greater tendency for symptoms of chronic ischemia to develop. The mortality rate and the incidence of necrosis increase with age and with arteriosclerosis, but chronic ischemia occurs less frequently. This demonstrates the importance of the state of the collateral circulation.

DIAGNOSTIC FEATURES

A patient with primary cardiac disease, who has fibrillation, and in whom a sudden onset of pain, coldness, and numbness in an extremity develops, must be regarded as having had an acute embolic episode until proved otherwise. It is surprising how often the early diagnosis is missed. Haimovici has emphasized the gradual onset in a significant number (18%) of these patients. In this survey 7%, also a significant number, had a more insidious onset. Pain was the commonest complaint, followed by coldness, numbness, discoloration, loss of motor power, and hyperesthesia or paraesthesia in that order of frequency. The diagnostic signs are absent pulses, coldness, discoloration, anesthesia, hyperesthesia, delayed capillary filling, and collapsed veins, also listed in order of frequency.

The pain is the severe persistent pain of ischemia. The pulse distal to the embolus is absent, and a blood pressure cuff or oscillometer may be necessary to determine the level of its disappearance. The pulse may be increased just above the embolus, and the site of the embolus may be tender. The extremity is cold by comparison with the other, and its color depends frequently on the time at which it is seen. Initially it is blanched owing to the absence of blood and the presence of arteriospasm not only in the major vessel but in the whole arteriolar system. This may be persistent or intermittent in character. Propagation of the clot takes place both distally and proximally to the site of the embolus so that eventually most of the arterial tree may become thrombosed. The veins are collapsed, but gradually the extremity takes on a mottled marble-like cyanosis, which progresses, as stagnation in the venous tree owing to lack of propulsive force supervenes. At this stage venous thrombosis occurs and is a bad prognostic sign with regard to ultimate

survival of the limb. Several of our patients died of pulmonary emboli. Although there are many factors involved, thrombosis of the deep veins as well as of the superficial veins is a natural consequence of the embolic episode and creates a potential source of danger to the outcome of the disease. Ischemic necrosis follows this thrombotic stage and gradually progresses to mummification of the extremity.

The vital signs are not significantly altered unless disaster is impending. In those patients admitted within 12 hours after onset, only 25% showed elevation of temperature, and in none was the temperature elevated above 38 C. The pulse rate was elevated in approximately 50%, and the respiratory rate increased in about 12%. The blood pressure and urine findings were related primarily to the cardiac or renal disease present and were of no diagnostic aid. Hemoglobin determinations showed no significant changes. A leucocytosis of 10,000 to 20,000 occurred in approximately 55%. Later, as the ischemia progressed to necrosis, the laboratory findings altered as expected.

TREATMENT

Therapeutic achievement is difficult to evaluate in these cases. Age, primary cardiac disease, state of collateral circulation, duration of time between onset and treatment, size, location, and multiplicity of emboli are all factors which cannot be detached from efforts directed primarily at the embolic episode. Experience and judgment may alter any single approach to the problem. Nevertheless, a few justifiable conclusions may be reached.

The shorter the time between onset of the embolic symptoms and the beginning of treatment the better will be the prognosis. Delay in diagnosis doubles the incidence of necrosis. Many of these patients are hospitalized at the time of their peripheral emboli because of cardiac difficulty or because of previous cerebral or visceral emboli. Of those patients with peripheral emboli who were seen during a current hospital stay or who were seen within six hours after the onset of symptoms, there were 30% who died, 10% in whom necrosis developed, and 60% who recovered. In contrast, of those patients who were seen later than six hours after onset of symptoms, there were 34% who died, 26% in whom necrosis developed, and 40% who recovered. Thus, the mortality rates were approximately the same. The mortality appears to be related more to the precarious cardiac status and the inability of the patient to withstand the added insults of ischemia or infarction alone or with indicated anesthesia and operative trauma. The incidence of necrosis, however, is more than doubled and the recovery rate is reduced by one-third in those whose treatment is delayed more than six hours.

Table 3 is an attempt to evaluate location and methods of therapy in 94 of the 106 acute embolic episodes. The 12 episodes excluded involved emboli to the renal, splenic, internal carotid, radial, gluteal, and other similar arteries.

Mesenteric.—All seven patients with superior mesenteric emboli died. Three underwent exploratory laparotomy; one, arteriotomy, embolectomy, and heparinization, and three received no treatment. Early diagnosis and operative intervention would seem to be the key to improve this situation.

Aortic.—Of 11 patients with embolism to the aortic bifurcation, 5 died. Three of these patients who died received only papaverine, one underwent embolectomy and died of pulmonary embolism, and one died with an associated superior mesenteric embolism. The other four patients underwent embolectomy; one had a result-

ing supracondylar amputation; one, amputation of the great toe, and two, complete recovery. All received anticoagulants, and one received continuous extradural block. Two of the patients with improvement received only anticoagulants, and one of these had lumbar paravertebral blocks in addition.

Iliac.—Of 10 patients with iliac emboli, 4 died. Of these four, two received anticoagulants and two underwent embolectomy. One patient, in whom the outcome was nonfatal, had a resulting amputation in spite of the administration of papaverine, anticoagulants, and spinal anesthesia, and the use of arteriotomy and periarterial stripping. Five patients improved, and all received anticoagulants. One underwent an unsuccessful embolectomy. In another patient, the clot was dislodged distally, and lumbar sympathectomy and periarterial stripping were done. Two had successful embolectomies.

Femoral.—Twenty-seven patients had femoral emboli. Seven died, one with complicating mesenteric embolism, and one patient died 12 hours following amputation. Two of the patients who died had no treatment, and two received only papaverine. Two were treated with anticoagulants, and one of these underwent embolectomy. Of the 20 patients who survived, 5 had a resulting amputation. One

TABLE 3.—*Summary of Location of Emboli and Therapy in 94 of the 106 Acute Embolic Episodes*

Location	No.	No Treatment	Anticoagulants	Blocks	Papaverine	Surgical	Died	Amputation	Improved
Superior mesenteric	7	3	1	0	0	4	7	—	—
Aortic bifurcation	11	4	5	3	4	5	5	2	4
Iliacs	10	0	8	5	4	7	4	1	5
Femoral	27	2	19	11	5	14	7	6	16
Popliteal	23	2	13	3	13	1	2	9	12
Tibial	5	1	3	1	2	0	1	0	4
Axillary	3	0	2	2	1	2	0	1	2
Brachial	8	1	4	2	3	2	3	1	4

of these patients was treated with heat and elevation, and four received anticoagulants. Embolectomy was performed on one of these patients with amputation. Of the 16 patients with improvement, 15 received anticoagulants. Eleven of these were treated with successful embolectomy. The following is a case presentation of successful and what we believe to be the indicated treatment.

M. B., a 51-year-old woman, was admitted to the University Hospitals of Cleveland from a neighboring community because of pain in the right leg. She had been under the care of her physician because of "heart trouble" for several months. A few weeks before admission, she had an attack of pain in the left leg that cleared spontaneously. Five hours prior to admission to the hospital, pain developed in the right leg, which became progressively severer. Past history revealed that the patient had juvenile chorea at the age of 10, with recurrences at the ages of 11 and 12 years. No arthritis was noted at that time. In 1942, nine years prior to admission, a left hemiparesis developed with some residual weakness. She had noticed exertional dyspnea for the past several months but denied orthopnea, edema, hemoptysis, or pleural pain. Two weeks prior to admission, she was digitalized by her family physician. Her family history and system reviews were noncontributory.

On physical examination the temperature was 36.4 F., pulse rate 60 and irregular, respiration rate 20, and blood pressure 110/60. The patient was a well-developed slightly obese white woman, who appeared acutely ill. The positive physical findings were confined to the heart and to the right lower extremity. The patient's pulse rate was irregular, with an apical radial pulse

deficit. The heart was enlarged to the anterior axillary line in the fifth intercostal space. The rhythm was grossly irregular. There was a Grade 3 harsh systolic mitral murmur and a Grade 2 aortic systolic murmur. There was a Grade 1 low-pitched diastolic murmur present at the mitral area.

Examination of the lower extremities revealed that there was blanching of the skin of the right leg below the knee, with a definite line of demarcation at that point. The left lower extremity had a reddish-purple cyanotic hue. Venous filling of the right extremity was markedly delayed. The veins in the right leg were collapsed, and the veins in the left leg were distended. Both femoral pulses were palpable, as was the left popliteal artery. The dorsalis pedis and the posterior tibial arteries were absent bilaterally. There was no palpable popliteal pulsation on the right, and the right femoral pulse was palpable to a point 2 in. (5 cm.) below the inguinal ligament. The laboratory data were as follows: hemoglobin 16 gm. per 100 cc., white blood cell count 16,800, and blood urea nitrogen 13.5 mg. per 100 cc. The urine gave a 1 + reaction for albumin. The electrocardiogram was read as showing auricular fibrillation, with an average ventricular rate of 80 and frequent ventricular premature beats. S-T and T changes over the precordium suggested left ventricular hypertrophy.

The diagnosis of rheumatic heart disease with auricular fibrillation and an embolus to the right femoral artery was made, and the patient was taken to the operating room, where skin-temperature readings were done. After control temperatures had been taken, a high spinal anesthetic was administered, and the temperatures were again determined at intervals up to 15 minutes. There was a prompt and satisfactory rise in the temperature of the left lower extremity but no improvement in the temperatures of the right leg. The patient was then prepared for embolectomy. A 5-in. (13 cm.) skin incision was then made in the femoral triangle over the common femoral artery. The artery was isolated and found to be occluded by an embolus at the junction of the superficial and profunda branches. Arteriotomy was done; the clot was extruded, and there was free flow from both directions. The arteriotomy was then closed, and the patient was heparinized. Immediately after surgery, the right leg became warmer than the left and remained so. The patient was maintained on intravenous injections of heparin, and bishydroxycumarin (Dicumarol) therapy was started. The prothrombin time was maintained below 30% during the hospital stay. The postoperative course was complicated by the development of a hematoma in the surgical incision, which resorbed spontaneously. The peripheral pulses on the right returned and remained palpable throughout the remainder of the hospital stay. She was given a salt-free diet and was discharged on her eighth postoperative day to the care of the local physician.

Popliteal.—Twenty-three popliteal emboli were treated. There were two deaths: One patient died of pulmonary embolism following amputation and one of cerebral embolism. In nine patients amputations were carried out. One of these patients was treated with elevation of the leg and application of hot packs alone, and in two the condition was complicated by femoral embolism. Two received no treatment, and four received only papaverine. Three of the patients with amputations received anticoagulants, and one underwent arteriotomy and periarterial stripping. Twelve patients improved. Of these, two received only papaverine, and one was treated by heat and elevation. All the others were treated with anticoagulants.

Tibial.—Five patients had emboli to the tibial artery. Of these, one died, and four improved. The patient who died had received only papaverine. Three of the improved patients received anticoagulants, and one received only hot stupes.

Axillary.—Three patients with axillary emboli were treated with anticoagulants, and two received stellate blocks. The same two underwent axillary artery embolectomy, and in one, amputation was carried out.

Brachial.—Eight patients had brachial artery emboli. Three patients died; of these, one received no treatment, and two received only papaverine. In one case,

unsuccessful embolectomy was followed by amputation. Of the four patients who recovered, all received anticoagulants; two had supplemental stellate blocks, and one had a successful embolectomy.

From this survey it may be seen that visceral emboli carry an extremely high mortality. Early diagnosis and early treatment may hold some promise in the future in these cases. Peripheral emboli are perhaps more amenable to treatment, and the results are being improved. In general, the more proximal the location of the peripheral embolus, the poorer will be the over-all prognosis. This is demonstrated by the results attained in saddle aortic emboli and common iliac emboli. Emboli usually lodge at the bifurcation of a major vessel, such as the iliac, femoral, or popliteal arteries. If the collateral circulation remains intact by patency of one of the large branches, then the outlook for viability of the limb is encouraging. However, if the clot is large enough or lodges in such a manner as to occlude both branches of the bifurcating vessel, then the prognosis is poor, unless operative removal is prompt.

In some of the early cases in this series, no treatment other than heat and elevation was administered. In the light of the pathophysiology, such treatment can only be condemned. Papaverine was then used routinely without any notable success. Perhaps intra-arterial administration of papaverine has value, but given intravenously, papaverine is useless. Recent evidence suggests that papaverine applied directly to the adventitia of a vessel may have some effect on myogenic spasm.[3] Anticoagulants are essential and are to be administered as early as possible, both to prevent thrombosis in the artery distally and proximally and to reduce the clotting tendency in the stagnated venous blood. The use of regional autonomic nervous system blockade is advised in order to relieve accompanying arteriospasm in the smaller arteries and arterioles which are under sympathetic control. These blocks have no effect upon spasm of the larger arteries, which is intrinsic and myogenic in origin.[4] An example of the use of spinal anesthesia in the successful treatment of femoral embolism follows.

G. R., a 45-year-old white woman, was admitted to University Hospitals of Cleveland on July 13, 1947, with a chief complaint of sudden numbness of the right leg. The present illness began approximately 12 hours before admission. The patient noticed sudden numbness of the right leg, which was followed by severe spasmodic pain. Shortly after the onset, the pain was treated by the application of heat, with some relief. She then again noted the loss of feeling from the knee down. Past history revealed that she had had a similar attack about 10 days before admission, which had disappeared rather promptly. She had had chorea as an adolescent and has had a known heart murmur for some five years prior to admission. Intermittently, for the past five years, she has been given digitalis.

On physical examination the temperature was 37.5 C., blood pressure 130/80, pulse rate 90 and irregular, and respiration rate 16. The positive physical findings were confined to the heart and to the right lower extremity. The heart was enlarged to the left and the rhythm was that of fibrillation with a small pulse deficit. Examination of the left lower extremity revealed that it was warm, and all pulses were palpable. The right leg was blanched at the base of the toes, and it was slightly cooler than the left. The right common femoral pulse was palpable, but the popliteal and dorsalis pedis and posterior tibial arteries were absent. Admission blood count and urine examinations were normal. The electrocardiogram was interpreted as showing auricular

3. Kinmouth, J. B.: Physiology and Relief of Traumatic Arterial Spasm, Brit. M. J. **1**:59-64, 1952.

4. Holden, W. D.: Acute Peripheral Arterial Occlusion; American Lectures Series, Number 141, Springfield, Ill., Charles C Thomas, 1952.

fibrillation with a ventricular rate at that time of 140, with occasional ventricular premature beats and digitalis effect. The diagnosis of chronic rheumatic heart disease with mitral stenosis and auricular fibrillation was made, with embolism of the right femoral artery.

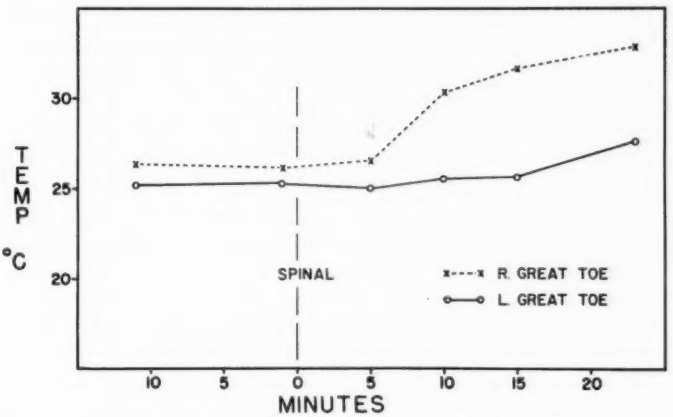
The patient was taken to surgery, where the right superficial femoral artery was exposed and was found to contain an embolus at the bifurcation. Arteriotomy was performed, and the embolus was removed. After removal of the embolus, there was a free flow of blood from the proximal end. A soft thrombus was removed from the distal portion of the artery. The arteriotomy wound was then closed, and the adventitia of the superficial femoral artery was stripped for a distance of 3 cm. Postoperatively the patient did well and was maintained on heparin and bishydroxycoumarin. The right foot remained warmer than the left, although no pulses could be palpated on the right. Sensation gradually returned to the right foot and leg, and she was discharged on her 12th hospital day, improved. She was maintained on digitalis, and bishydroxycoumarin therapy was continued on an ambulatory basis under careful supervision of her physician.

Some three years later, on April 24, 1950, the patient was again admitted to the hospital, complaining of pain in the left leg and hip. Four hours prior to admission, she experienced a sudden deep pain in the left groin, radiating down to the left knee, which lasted about 30 minutes. After that she noticed crampy pain in the left buttock, and numbness of her toes developed. Physical examination revealed a temperature of 37 C., pulse rate 80, blood pressure 150/80, and respiration rate 18. The patient was a well-developed well-nourished white woman appearing acutely ill. The positive physical findings were confined to the heart and the extremities. The heart findings were approximately the same as on the previous admission. Examination of the extremities revealed that the femoral pulse was perceptible on the left but was of much less amplitude than that on the right. The peripheral pulses on the right were absent as were the popliteal, posterior tibial, and dorsalis pedis on the left. The temperature readings and oscillometric readings done in the patient's room showed decreased temperature and absent pulsations in the left lower extremity. The patient was taken to surgery, and a high spinal anesthetic was given. The temperature readings were done before and after the anesthetic. There was an immediate rise of 4½ degrees in the left foot, with a return of color, warmth, and venous filling, and it was decided that there had been an arterial embolus to the left side of the pelvis and hip with associated vasospasm of the left femoral artery. The patient was then returned to her room and was given heparin and bishydroxycoumarin, as well as (Priscoline) 2-benzyl-4,5-imidazoline hydrochloride, 25 mg. every six hours. The patient's hospital course was good; the pulses returned to the left leg and foot, and she was discharged on her 11th hospital day. She was maintained on bishydroxycoumarin on an ambulatory basis by her private physician.

One year later, May 5, 1951, this patient was again seen because of sudden sharp pain in the right calf and foot, coldness of the leg, anesthesia, and muscle paralysis. She had been maintained on bishydroxycoumarin since her previous admission up until some two months prior to admission. Bishydroxycoumarin therapy was discontinued at that time because of hematuria. Two hours prior to admission, while walking, the patient noticed the onset of a severe cramping pain in the right leg and thigh. Shortly afterward she was unable to walk and noticed numbness and pain in the right leg, and the right leg and foot felt cool. The positive physical findings were as follows: temperature 37 C., pulse rate 76, blood pressure 112/78, and respiration rate 20. The findings on physical examination were essentially unchanged from the previous admission, except for the lower extremities. There was diminished temperature in the right foot and leg, and venous filling was delayed. There was anesthesia to a point just below the right knee. There were no peripheral pulses palpable in either lower extremity, except for a palpable left femoral artery. The left leg was warm, however, and otherwise normal. The patient was taken to surgery, and, after control temperature readings were done, a spinal anesthetic was administered. After some 35 minutes, the temperatures in the right toes and foot became elevated 6 degrees C., and there was a satisfactory response in color and venous filling (Chart). It was felt therefore that this patient had a small embolus on the right, with a marked degree of associated vasospasm. She was given 50 mg. of heparin intravenously and was returned to her room, with the head of the bed elevated 6 in. (15 cm.). The numbness and paresthesia gradually disappeared in the postoperative period. She was maintained on bishydroxycoumarin and was discharged on the 11th hospital day.

Approximately one year later, on April 25, 1952, she had severe cramp-like pain in the lower right leg without any numbness or color changes, which was relieved by the application of heat and by administration of acetylsalicylic acid. Examination in the office at that time revealed no essential change from previous examinations, and in view of the multiple emboli and the increasing exertional dyspnea, the patient was advised to have a work-up for evaluation of commisurotomy. She was readmitted to the hospital on April 29, and after cardiac evaluation, a mitral commisurotomy was carried out, with the use of general oxygen-ether anesthesia, by Dr. Claude Beck. The atrial appendage was amputated, and it was interesting to note that no mural thrombi could be found. Her postoperative course was uneventful, and she was discharged on the ninth postoperative day, improved. A follow-up reveals that the patient is symptomatically much improved but still has claudication of the legs.

Embolectomy should be performed on the larger arteries. Our results seem to indicate it is not to be attempted in cases of popliteal and possibly brachial artery embolism. Interruption of collateral circulation by surgery may be sufficient to



Release of vasospasm in right lower extremity after administration of spinal anesthesia in Patient G. R. Left lower extremity, site of a previous embolus, was not affected.

further embarrass the extremity and lead to amputation. We have had no experience with arteriectomy at the site of the embolism. The use of arteriograms may offer some valuable aid in the diagnosis of the site of the embolism and may be of some aid in differentiating occlusion by embolus from occlusion by spasm. Perhaps the use of aortograms may prove helpful in the localization of saddle and iliac emboli, but we feel that the routine use of arteriograms, however, is unnecessary and that accurate localization can be made by clinical methods.

SUMMARY

Eighty-five cases of visceral and peripheral arterial emboli, in which the patients were admitted to the University Hospitals of Cleveland during the past 18 years, are reviewed.

A primary cardiac disturbance, either anatomical or functional, was present in 95% of these cases. Auricular fibrillation was the common functional disturbance and was present in 80% of these cases.

The prognosis as to both life and limb is discussed in terms of primary cardiac disease, age of the patient, location and multiplicity of emboli, and time and type of treatment instituted. The single most important prognostic feature is the state of the collateral circulation.

The pathological and physiological changes occurring during an acute embolic episode are discussed in relation to rational therapy.

Early recognition and therapy are paramount, and the use of anticoagulants is essential. The use of regional autonomic blockade for alleviation of accompanying small arterial and arteriolar spasm is emphasized. Embolectomy is to be performed on the larger arteries.

MAINTAINING VIABILITY OF AN EXTREMITY WITH ACUTELY OBSTRUCTED ARTERIAL CIRCULATION

Arterial Autoperfusion Method: Preliminary Report

RAYMOND GREEN, M.D.
CHICAGO

THE FREQUENCY of loss of limb because of embolic occlusion is substantially high, due either to inability or failure to counteract the ill effects resulting therefrom. Also, the chance for survival following restoration of the circulation after embolectomy depends upon the length of time the extremity has been deprived of its blood supply. Since the ill effects of embolic occlusion (ischemia and gangrene) are primarily due to the absence of adequate blood supply peripherally, it seemed a fundamental concept that if oxygenated blood could be supplied to the limb peripheral to the embolus the limb should survive.

Since the fundamental concept is to supply oxygenated blood to that part which has been denied it and thus "restore" the circulation, the autoperfusion of arterial blood from an upper extremity into an artery peripheral to the embolus suggested itself. This procedure would thus establish a circuit of arterial blood. It is intended to accomplish this by a circuit in which one end of a plastic tube is inserted into the radial (donor) artery, the other end of the tube being placed into the obstructed (recipient) artery peripheral to the embolus, as the posterior tibial artery.

This procedure was tested experimentally in six normal, fasting, mongrel anesthetized dogs.

METHOD

The dogs were anesthetized with pentobarbital sodium solution, 25 mg. per kilogram of body weight. The temperature of the foot pads was then recorded. In all dogs, both femoral arteries were ligated. It was found necessary because of the normal extensive collateral blood supply to the limbs to ligate the iliac arteries in addition; in two dogs the aorta just above the bifurcation was also ligated. These additional ligations effectively obstructed the blood flow to the extremities. The autoperfusion was accomplished by cannulating the brachial artery (in two experiments the carotid artery was used instead) and the femoral artery distal to the ligation. A plastic tube was used to connect the two cannulae, and blood was permitted to flow from the "donor" artery to the "recipient" femoral artery under arterial pressure. Heparin solution was placed in the plastic circuit and was also injected intravenously. In some experiments the tubing was wrapped in cloth to prevent dissipation of heat. An estimate of the efficiency of the blood flow to the distal portion of the extremity was then obtained by again measuring the temperature of the foot pads at regular time intervals. The total period of observation in these experiments averaged about eight hours.

Read before the Chicago Surgical Society, Chicago, Nov. 6, 1953.

Clinical Assistant Professor of Surgery, University of Illinois College of Medicine (Dr. Green).

From the Cardiovascular Department, Medical Research Institute, and the Department of Surgery, Michael Reese Hospital.

RESULTS

After ligation of the blood supply to the hind limbs, the temperature of the foot pads gradually fell to approximately the level of room temperature, indicating objectively the inadequacy of the blood supply to these parts. With the institution of the autoperfusion, the temperature of the foot pad of the perfused limb, in all animals, gradually and progressively rose to preligation levels, reaching the normal value within approximately one hour. This normal temperature level was maintained for the entire period of observation. In some experiments the temperature showed a decline later associated with the decline in the body temperature as revealed by the rectal temperature. The temperature of the foot pad of the untreated occluded (control) limb, on the other hand, remained at approximately the environmental temperature throughout the procedure.

In two experiments, clotting inadvertantly occurred within the tubing, resulting in cessation of the blood flow. In both instances there was a fall in the temperature

TABLE 1.—*Data from a Typical Experiment (Dog 2588)*

Time	Temperature, C.				
	Room	Rectal	Front Pad	Hind Pad (Control)	Perfused Extremity Foot Pad
9:00 a. m.	24.0	38.5	36.5	35.8	35.0
10:00 a. m. (ligation)	....	....	....	....	....
11:00 a. m.	24.8	37.0	36.0	31.8	30.8
11:10 a. m. (autoperfusion started)	....	....	....	....	....
12:00 noon	24.5	36.0	35.0	31.8	35.8
1:00 p. m.	25.0	35.0	33.6	27.8	34.2
2:00 p. m.	25.2	34.8	32.0	26.6	32.6
3:00 p. m.	25.5	34.8	28.8	25.5	30.6
3:30 p. m. (window opened; dog shivered at 3:45 p. m.)					
4:00 p. m.	22.8	34.2	25.8	23.0	28.6
5:00 p. m.	21.0	34.0	24.5	21.5	26.0
6:00 p. m.*	21.2	34.0	24.7	21.0	24.5
7:00 p. m.	20.0	34.0	24.4	20.2	26.6

* Clot found in catheter; catheter flushed and perfusion continued.

of the foot pad. After removal of the clot and reestablishment of the blood flow, the temperature of the foot pad rose again.

The data of one typical experiment are presented in the Table.

COMMENT

These experiments demonstrate the validity of the concept that autoperfusion of arterial blood can maintain the viability of an extremity, the blood supply of which is acutely obstructed. They further demonstrate that the procedure is feasible.

It seems possible that this method has implications other than those concerned with embolic occlusion. In some patients, even after apparently successful embolectomy, failure may follow because of subsequent thrombosis peripheral to the embolus. Also, there are times when differentiation between embolic occlusion and other phenomena, such as primary thrombosis, the presence of a small embolus with incomplete occlusion, or spasm secondary to thrombosis, may be difficult. Surgical intervention may actually not have been indicated, and thus, having been undertaken, may be deleterious. On the other hand, when the diagnosis is not clear, temporizing may be disastrous if it is ultimately proved that an embolus was present. The use of this new procedure during the period of observation can do little harm. Much

needed time is provided for careful differential diagnosis. More important, it provides an opportunity for definitive treatment beyond the presently accepted optimum period, measured in hours. It is conceivable that the autoperfusion can be continued long enough for the formation of collaterals.

The method presented may also be useful in cases in which an artery is severed as a result of injury. It could serve as an interim procedure until the artery can be reconstituted by anastomosis, vein graft, or other appropriate method. This suggests possible application in military as well as in civilian surgery and allows final correction to be delayed for more opportune circumstances.

SUMMARY

A concept was developed that autoperfusion of arterial blood could maintain the viability of an extremity with an acutely obstructed or with an acutely developed inadequate blood supply. This concept was tested experimentally in the dog. Under the conditions of the experiments, the validity of the concept has been proved. Autoperfusion of arterial blood can maintain the viability of an extremity. This new procedure may offer a simple surgical approach to some of the problems concerned with embolic occlusion. Its application in other entities is discussed. The results obtained justify the plan to test this method clinically.

104 S. Michigan Ave.

Dr. Simon Rodbard, Assistant Director of the Cardiovascular Department, gave encouragement and valuable suggestions during this study.

Dr. Louis N. Katz, Director of the Cardiovascular Department, gave advice.

Mr. Francis Williams, B.S., gave technical assistance.

NATURE OF LIVER FAILURE DUE TO COMPLETE BILIARY OBSTRUCTION

CHARLES A. MACGREGOR, M.D.
DENVER

THE CARE of a patient with obstructive jaundice still remains a challenge to the surgeon's judgment and skill. With our increasing knowledge of the effect of operation on the metabolic response of the patient we now have a much better understanding of the significance of the term "surgical risk" than ever before. The manner in which the patient with obstructive jaundice is prepared for surgery, however, still demands improvement. Some of these patients continue to die of liver failure in the immediate postoperative period, owing either to inadequate preparation or to the limitations of our knowledge at present.

The following study was carried out to determine the nature of liver failure in the presence of complete biliary obstruction. Emphasis has been placed upon serial tests of several liver functions rather than upon pathological examination of the tissue.

Effort has been made to correlate the times of appearance of impairment of the individual functions of the liver as well as the progress of the degree of impairment.

The study reported herein is based solely on the careful sequential observation of six dogs with simple, uncomplicated, biliary obstruction. It has been the conviction of my colleagues and I, from a review of the literature, that a study of the simplest possible form of extrahepatic biliary-tract obstruction should be carried out to provide a basis for further studies on the interrelations of obstruction, infection, liver cell disease, kidney disease, and other multivisceral conditions.

PRESENT INVESTIGATION

A series of nine healthy normal dogs varying in weight from 13 to 18 kg. were studied preoperatively. They were then operated upon with use of intravenous injections of pentobarbital sodium anesthesia (0.032 gm. per kilogram body weight). The operation consisted of ligation and division of the common duct and a biopsy of the liver. Care was taken to divide the common duct very close to the duodenum

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This material has previously been reported in part. (Macgregor, C. A.: A study of Liver Function in the Dog with Complete Biliary Obstruction, Surgical Forum: American College of Surgeons, 1952, Philadelphia, W. B. Saunders Company, p. 399).

From the Department of Surgery, Peter Bent Brigham Hospital, and the Laboratory for Surgical Research, Harvard Medical School. This study was aided by a grant from the American Cancer Society and a grant in memory of Mary B. Claff.

to avoid missing any low entering tributary bile duct and to interpose omentum between the divided parts of the common duct. Postoperatively periodic studies were carried out until either death occurred or the animals were killed. The latter was done in the terminal stages in the presence of imminent death to obtain fresh specimens of liver for glycogen and fat stains. Complete autopsies were done on all animals. During the entire period of study all of the dogs were fed once daily. Their diet consisted of a mixture of Ken-L-Biskit (The Quaker Oats Company) and Pure Lard (Armour & Company). The mixture was such that each dog received daily approximately 35 gm. of protein, 65 gm. of fat, and 105 gm. of carbohydrate. Their total caloric intake thus consisted of approximately 1,200 Cal. as a maximum. As a general rule all of this was eaten by each dog, except during the terminal few weeks. The diet contained adequate amounts of riboflavin, cynanocobalamin (vitamin B_{12}), animal liver, vitamin D, and iodized salt.

Six of the nine dogs were considered satisfactory for analysis. Three died in the early postoperative period, one of an accidental overdose of anesthesia, one of hemorrhage from the site of liver biopsy, and one of generalized suppurative peritonitis. They are of value only so far as they furnish additional information as to normal values of the multiple preoperative tests.

The remaining six dogs afforded complete studies and are reported on in Charts 1 to 6 and in Tables 1 to 7.

I. *Protein Metabolism.*—1. Historical Background: The relation of protein metabolism to liver disease in general has been well established both clinically and experimentally. Sherlock [1] found in a study of 49 patients with complete biliary obstruction that 12 had a lowered total serum protein. This was attributed to a fall in serum albumin, with the globulin remaining almost unaltered. In recent years a number of reports of electrophoretic analyses of the serum protein in patients with liver disease have been made.[2] Many of these include data on patients with common duct obstruction. Popper [2c] found in 26 cases of extrahepatic biliary obstruction that the serum albumin was less than 3.5 gm. per 100 cc. in all but 2 cases. The mean was 2.62 gm. per 100 cc., as contrasted with the mean of his control normals which was 4.39 gm. per 100 cc. He also found the serum globulin to be elevated, with a mean of 4.08 gm. per 100 cc. in contrast with the mean of his control normals which was 2.70 gm. per 100 cc. Electrophoretic analysis of the globulin fraction revealed that the elevated total globulin was for the most part

1. Sherlock, S. P. V.: Biochemical Investigations in Liver Disease: Some Correlations with Hepatic Histology, J. Path. & Bact. **58**:523 (July) 1946.

2. (*a*) Franklin, M.; Bean, W. B.; Paul, W. D.; Routh, J. I.; de la Huerga, J., and Popper, H.: Electrophoretic Studies in Liver Disease: II. Gamma$_1$ Globulin Chronic Liver Disease, J. Clin. Invest. **30**:729 (July) 1951. (*b*) Gray, S. J., and Barron, E. S. G.: The Electrophoretic Analysis of the Serum Protein in Diseases of the Liver, J. Clin. Invest. **22**:191 (March) 1943. (*c*) Popper, H.; Bean, W. B.; Huerga, J. de la.; Franklin, M.; Tsumagari, Y.; Routh, J. I., and Steigman, F.: Electrophoretic Serum Protein Fractions in Hepatobiliary Diseases, Gastroenterology **17**:138 (Feb.) 1951. (*d*) Ricketts, W. E., and Sterling, K.: Comparative Studies of "Liver Tests" and Electrophoretic Analyses of Serum Protein in Portal and Biliary Cirrhosis, Am. J. M. Sc. **221**:38 (Jan.) 1951. (*e*) Verschure, J. C. M., and Janssen, L. W.: Correlation Between Liver Function and Serum Protein Distribution, Acta Hemat. **4**:186 (Sept.) 1950.

due to elevation in the beta and alpha fractions. The gamma globulins were within normal range. The beta globulin, for example, was elevated in 73% of his cases of extrahepatic obstruction. This in general has been the experience of others.[3]

From a search of the literature there is apparently no report of a similar study on an experimental basis. It would seem important to know whether these changes in the serum protein fractions are the result of simple obstruction or whether cholangitis plays a role.

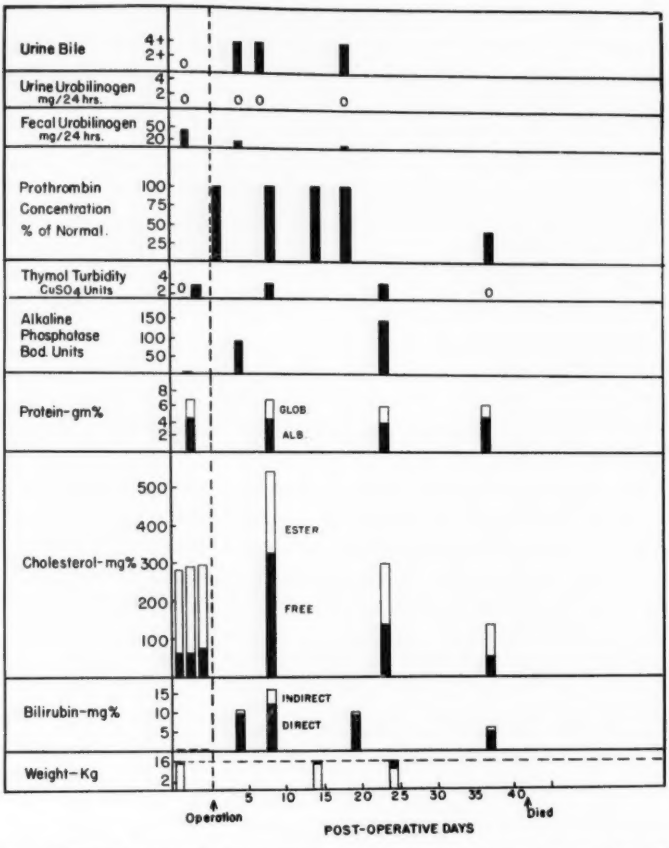

Chart 1.—Composite graph of preoperative and postoperative course of Dog BL 126-51 with complete common duct obstruction.

2. Method: The micro-Kjeldahl method of analysis has been used throughout.[4] Serum nonprotein nitrogen levels were also obtained by means of this method and served to indicate renal function.

3. Footnote *2b-d*.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Volume II: Methods, Baltimore, Williams & Wilkins Company, 1932, p. 691.

TABLE 1.—*Summary of Data on Dog BL 126-51*

Day #	Wt. Kg.	Bilirubin mg.% Dir.	Bilirubin mg.% Ind.	Cholesterol Ester mg.%	Cholesterol Ester %	Cholesterol Total mg.%	Thymol Turbidity $CuSO_4$ Units	NPN mg. %	Protein (gm.%) Total	Protein (gm.%) Alb.	Protein (gm.%) Glob.	Alk. P'tase Bod. Units	Prothrom. % conc. of normal	Urine Bile	Urine Urobilin. mg/24°	Feces Urobilin. mg/24°
Pre-Op.	15	0.25	0.0	206.2	72	287.0	0.05	33.0								
		0.12	0.12	213.0	73	293.0	0.0		8.63							
		0.24	0.24	212.5	71	300.0	3.5	24.1	6.74	4.21	2.53	0.9		0	0	44.1
Operation: Biopsy of Liver, Ligation and Division Common Duct																
P.O. 4		10.2	1.2									89.8	100	4+	0	15.0
8		12.6		225	41	550.	4.0	23.0	6.53	4.00	2.53		100	4+	0	0.3
14	13.5												100			
18													100	4+	0	4.2
19		9.9	0.9													
23				162.5	53	300.	4.0		5.69	3.45	2.24	140.2				
24	12.2															
37		5.4	0.6	67.5	63	137.5	0.	23.0	5.82	4.31	1.51		40			
41	Died															

Autopsy (Approximately 6 weeks post. op.)

Thin, emaciated, jaundiced. Abdominal skin discolored with brownish-greenish stain. Thoracic cavity normal. Abdominal cavity filled with 1000 cc. of brownish fluid. Orange soft exudate on serosal surfaces. Easily wiped off. Predominantly in Right Upper Quadrant. Stomach, small bowel, and colon all markedly contracted. Lumen contained dark unclotted bloody fluid along entire course. Hemorrhagic gastritis. Liver dark green, smooth. Weight 320 grams. Cut surface dotted with dark green dilated bile ducts. Gall bladder filled with dark green bile. No stones. Much precipitated pigment. Common duct system greatly dilated. No evidence of leak or perforation of biliary system. No connection between proximal common duct and the small bowel. In the duodenum there were three ulcers which may have been the site of some bleeding as well as the stomach. Ulcers were deep and with very little reaction to them. Distal common duct had its ligature in position and distal to it was quite patent.. Kidneys normal.

Microscopic sections of liver at autopsy showed typical biliary cirrhosis with moderate fibrosis and bile stasis. Fat stains showed moderate infiltration. There was no evidence of cholangitis or hepatitis.

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3. Results: It is apparent from the Tables that there is a gradual decrease in the serum albumin and eventually a reversal of the albumin-globulin ratio. Of the four dogs who survived eight weeks or longer (Charts 3 to 6; Tables 3 to 6) all showed a progressive fall in the level of the serum albumin to values below 3 gm. per 100 cc. These four also showed a gradual rise in the serum globulin, which in three dogs reached a level about 3 gm. per 100 cc. In these same four dogs there was a reversal of the albumin-globulin ratio at a point about eight weeks following

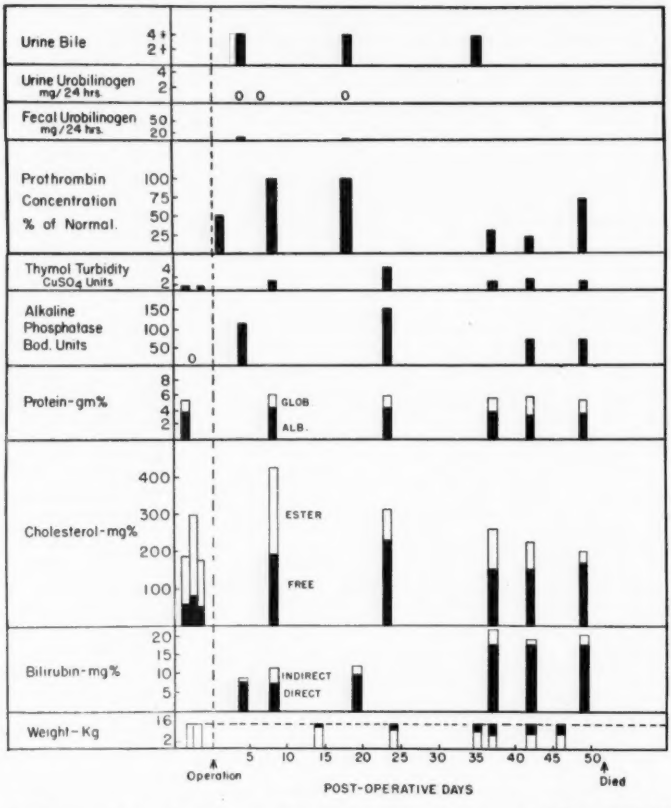

Chart 2.—Composite graph of preoperative and postoperative course of Dog WH 128-51 with complete common duct obstruction.

the obstruction of the common duct. In the two dogs surviving only six and seven weeks, respectively, these changes were not found (Charts 1 and 2; Tables 1 and 2). The nonprotein nitrogen levels remained within normal range throughout the course in all six dogs.

4. Comment: One of the more significant observations made in the present study has been the inexorable fall in the level of the serum albumin, with the eventual reversal of the albumin-globulin ratio. This has been noted clinically in

TABLE 2.—*Summary of Data on Dog WH 128-51*

Day #	Wt. Kg.	Bilirubin mg.% Dir.	Bilirubin mg.% Ind.	Cholesterol Ester mg.%	Cholesterol Ester %	Cholesterol Total mg.%	Thymol Turbidity $CuSO_4$ Units	NPN mg. %	Protein (gm.%) Total	Protein (gm.%) Alb.	Protein (gm.%) Glob.	Alk. P'tase Bod. Units	Prothrom. % conc. of normal	Urine Bile	Urine mg/24°	Feces Urobilin. mg/24°
Pre-Op.		0.12	0.	131.2	70	187.5	1.0	29	5.60							
"		0.12	.12	218.7	73	300	0.0	33	5.1	3.59	1.87					
"	13.6	0.12	0	129.0	71	175	1.0	41	5.46			0				
	Operation: Ligation and Division Common Duct															
P.O. 1													50			
4		8.0	0.8									113.5		4+	0	10.0
8	12.6	7.8	3.6	237.5	56	425	2.3	26	6.11	4.18	1.93		100	4+	0	0.3
18		9.9	2.1										100	4+	0	7.05
23	11.2			87.5	28	312.5	6.5		6.06	4.18	1.88	155.5				
37	8.9	18.0	3.6	112.5	42	262.5	2.5		5.84	3.73	2.11		28	4+	0.3	
42	8.7	18.0	1.2	75.	33	225.0	3.0		5.76	3.29	2.47	72.8	20			
49	8.2	18.0	2.4	31.2	15	200.0	2.5		5.40	3.45	1.95	71.7	70			
51	Died															

Autopsy (Approximately 7 weeks post. op.)

Thin wasted animal with obvious jaundice. Almost no subcutaneous fat. Lungs, pleural cavities, heart normal. Peritoneal cavity contained about 100 cc. of bile-stained fluid. Peritoneum dull but without exudate. Stomach and intestines contracted but pink. Liver weight 250 gm. greenish brown smooth with sharp edge. Gall bladder huge contained 100 cc. of very dark greenish bile. Common duct markedly dilated and communicated freely with gall bladder. No communication with intestine. No area of leak or perforation. Stomach showed hemorrhagic gastritis. Small intestine contained only a milky white fluid. Colon contained a few concretions of black dry guaiac positive feces.

Sections for microscopic examination were lost through accident.

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patients with biliary obstruction, as previously mentioned, but in such cases it has been difficult to prove whether such changes were the result of the obstruction or of complications thereof, such as mild inflammatory hepatocellular disease. The rise in the globulin among most of the dogs is also of interest in view of the above clinical experience.

The cause for the fall in serum albumin is not entirely clear. Much of it undoubtedly is due to impaired ability of the liver cell to synthesize it from absorbed amino acids, but some of the difficulty may be due to impaired absorption, since

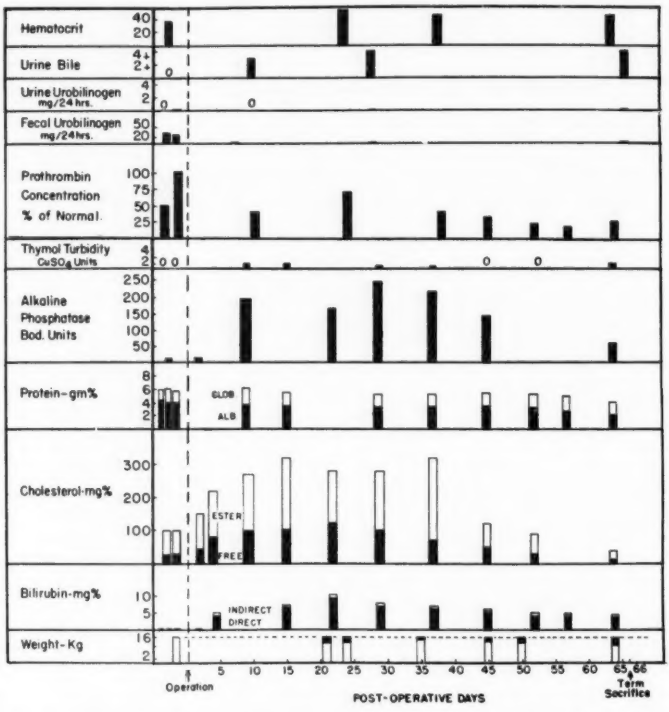

Chart 3.—Composite graph of preoperative and postoperative course of Dog SP 19-52 with complete common duct obstruction.

Canonico and Mann [5] have observed a marked decrease in activity of the jejunum following obstruction of the common bile duct. In the present study the dietary intake of protein was satisfactory throughout all but the terminal stages of the postoperative course. The administration of parenteral amino acids might resolve this problem.

II. *Carbohydrate Metabolism.*—1. Historical Background: Extensive studies on carbohydrate metabolism in rats with experimental extrahepatic biliary obstruc-

5. Canonico, A., and Mann, F. C.: Intestinal Activity After Obstruction of Common Bile Duct. Surgery **13**:81 (Jan.) 1943.

TABLE 3.—*Summary of Data on Dog SP 19-52*

Day #	Wt. Kg.	Bilirubin mg.% Dir.	Bilirubin mg.% Ind.	Cholesterol Ester mg.%	Cholesterol Ester %	Cholesterol Total mg.%	Thymol Turbidity $CuSO_4$ Units	NPN mg. %	Protein (gm.%) Total	Protein (gm.%) Alb.	Protein (gm.%) Glob.	Alk. P'tase Bod. Units	Prothrom. % conc. of normal	Urine Bile	Urine mg/24°	Feces Urobilin, mg/24°
Pre-Op.	18.2	0.24	0.	75.	75	100	0	21.9	5.85	4.28	1.57	2.4	50	0.	0.	30.6
"	17.6	0.12	0.12	69.9	69.9	100	0	22.2	5.79	4.04	1.75		100	0.	0.43	23.8
"	16.8	0.12	0.					21.5	5.59	3.91	1.68					
Operation: Biopsy of Liver, Ligation and Division Common Duct																
P.O.																
2		0.12	0.12	107.5	72.0	150						15.6				
4		4.3	0.7	140	64	220										
9				170	63	270	2.0	16.0	6.21	3.71	2.50	193.6	40	3+	0	0.8
15		7.0	0.2	220	69	320	2.0	21.0	5.41	3.56	1.85					
22	14.2	9.6	1.0	160	57	280		26.0	5.43			167.5	70			
29	15.3	7.2	0.6	180	64	280	1.0	26.0	5.15	3.45	1.70	244.8		4+	0.23	1.0
37	15.3	6.9	0.3	250	78	320	0.5	21.0	5.16	3.21	1.95	207.0	40			
45		5.4	0.6	70	58	120	0.	20.0	5.43	3.35	2.08	140.2	33			
52	13.0	4.2	0.6	60	67	90	0.	16.0	5.08	2.99	2.09		23			
57	11.8	4.3	0.5	60	71	85	0.5	21.0	4.67	2.47	2.20		19			
64	11.0	3.6	0.6	27	71	38	0.8	21.0	3.91	1.73	2.18	54.2	28	4+	0.23	0.2
65	Terminal Sacrifice (approximately 9 weeks post. op.)															

Autopsy

Extreme emaciation. Jaundiced. The abdomen was opened showing no free fluid. The serosal surfaces were yellowish pink, glistening, and smooth. The liver which weighed 310 gms. was dark greenish brown in color. The gall bladder and bile ducts were dilated two to three times normal size. Disection revealed no connection between the biliary system and the intestine. The small bowel and stomach contained a colorless opaque viscid fluid. The colon contained gray feces with a thin brown outer layer. Kidneys, pancreas, stomach, heart, lungs were normal.

Microscopic sections of the liver biopsy taken at operation showed no evidence of pathology. Autopsy sections showed typical biliary cirrhosis with considerable fibrosis, dilated bile canaliculi and bile stasis. Glycogen stains showed remarkably little loss of glycogen. There was no evidence of cholangitis or hepatitis.

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tion have been carried out by Edlund.[6] He found that in total biliary stasis there was a progressive decrease in the glycogen content of the liver, hyperketonemia, and a decreased level of blood sugar. This was thought due to increased glycogenolysis. Treatment with parenteral glucose increased the glycogen content of the liver. Snell and his associates[7] found a slight but definite impairment in fructose metabolism by use of the oral fructose tolerance test in their obstructive experiments

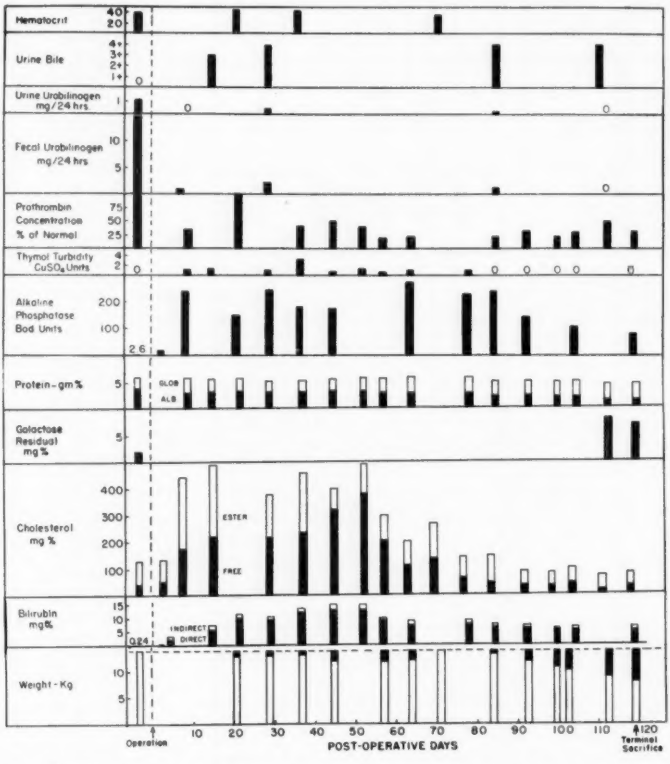

Chart 4.—Composite graph of preoperative and postoperative course of Dog KI 24-52 with complete common duct obstruction.

on dogs. In 1941 Bassett, Althausen, and Coltrin[8] called attention to the intravenous galactose tolerance test as of value in differentiating obstructive from

6. Edlund, Y.: Studies on the Carbohydrate Metabolism and Liver Protection Therapy in Experimental Extrahepatic Biliary Obstruction, Acta. chir. scandinav. (Supp. 136) **96**:187, 1948.

7. Snell, A. M., Greene, C. H., and Rountree, L. G.: Diseases of the Liver: II. A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, Arch. Int. Med. **36**:273 (Aug.) 1925.

8. Bassett, A.; Althausen, T. L., and Coltrin, G. C.: A New Galactose Test for Differentiation of Obstructive from Parenchymatous Jaundice, Am. J. Digest. Dis. **8**:432 (Nov.) 1941.

TABLE 4.—*Summary of Data on Dog KI 24-52*

Day #	wt. Kg.	Bilirubin mg.% Dir.	Bilirubin mg.% Ind.	Cholesterol Ester mg.%	Ester %	Total mg.%	Thymol Turbidity $CuSO_4$ Units	NPN mg. %	Protein (gm.%) Total	Alb.	Glob.	Alk. P'tase Bod. Units	Prothrom. % conc. of normal	2 hr. Galact. resid. mg.%	Urine Bile	Urine Urobilin mg/24°	Feces Urobilin mg/24°
Pre-	14.6	0.12	0.12	87.5	70	125.0	0	27.2	6.26	3.84	2.42	2.6	100	2.0	0	0.13	15.1
Op.	14.2	0.12	0.12					23.0	5.66	3.51	2.15						
		0.24	0.	90.0	69	130.0	0.	20.0	6.50	4.21	2.29						
Operation: Biopsy of Liver, Ligation and Division Common Duct																	
P.O.																	
2		0.24	0.24	90.0	64	140.0						17.5					
8		6.6	0.3	275.0	61	450.	1.0	23.0	5.66	2.94	2.62	234.0	70		3+	0.	1.0
14		6.7	0.5	280.0	56	500.	1.0	26.0	5.69	3.16	2.53						
20	13.1	10.1	0.9					27.0	5.71	3.41	4.30	148.0	100				
28	13.4	9.6		165.0	43	380.	1.0	31.0	5.21	3.11	2.10	245.7			3+	0.11	2.4
36	13.1	12.3	0.9	224.0	49	460.	3.0	29.0	5.43	2.98	2.45	183.3	40				
44	12.3	13.2	1.8	80.0	20	400.	0.5	29.0	5.49	3.28	2.21	175.2	50				
51		13.2	1.8	140.0	27	520	1.0	23.0	5.71	3.16	2.55		40				
56	12.	9.0	0.6	100.	33	300	0.5	23.0	5.61	2.67	2.94		19				
63	12.3	6.98	1.98	92.	45.5	202	1.3	27.0	5.83	2.53	3.30	271.4	23				
*70	14.0			136.	50.0	268											
77	13.8	7.47	2.10	77.	53.0	146	1.6	25.0	5.58	2.62	2.96	230.8					
84		6.6	0.6	100.	67.0	150	0.	17.0	5.11	2.32	2.79	239.9	20		4+	0.33	1.45
92	12.1	6.0	0.1	57.5	64.0	90	0.	14.0	5.06	2.45	3.61	140.8	33				
**99	10.9	5.7	0.3	52.5	62.0	85	0.	17.0	4.83	2.18	2.65		23				
104	10.2	5.1	0.9	57.5	57.5	100	0.	16.0	4.90	2.14	2.76	104.8	33				
107	BUN= 10 mg.%, Na= 146 mEq/L, K= 4.7 mEq/L, Cl= 123 mEq/L.																
112	9.2			55.	73.0	75		30.0	4.53	1.69	2.84		50	8.0	4+	0.	0.
119	8.2	5.9	0.7	47.5	59.0	80	0.	27.0	4.71	1.71	3.0	84.2	33	7.2			
119	Terminal Sacrifice(17 weeks post. op.)																

* Ascites appeared ** Ascites disappeared

Autopsy

Weight 8.2 Kg. Extreme emaciation. Jaundiced sclerae and skin. Lungs, heart, and pleural spaces normal. Peritoneum no excess fluid or signs of inflammation. Liver small, rough, and firm, dark greenish. (weight 271 gm.) Gall bladder markedly distended, taut, thin-walled and greenish blue. No evidence of perforation. Divided ends of common duct separate and not patent. Stomach and small intestine contained colorless opaque fluid with no evidence of bile. Colon feces formed grayish brown. Kidneys and pancreas normal. Striking absence of fat. Microscopic sections of the liver biopsy taken at operation showed no evidence of pathology. Autopsy sections showed typical changes of biliary cirrhosis with moderate fibrosis and bile stasis. Fat stains showed moderate to extensive fatty infiltration and glycogen stains showed only moderate loss of glycogen. There was no evidence of cholangitis or hepatitis.

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parenchymatous jaundice. Sherlock [1] in applying the test to patients with progressive obstructive jaundice found that the test became positive only in the terminal stages of the disease. There are also the clinical experiences of Ivy,[9] Zieve [10] and Colcher and his associates [11] which indicate that there is relatively little impairment in hepatic metabolism of galactose in patients with obstructive jaundice and frequently considerable impairment in patients with hepatocellular disease.

Because of its obvious value in differentiating between clinical obstructive and nonobstructive jaundice, it would seem helpful to know in which circumstances the

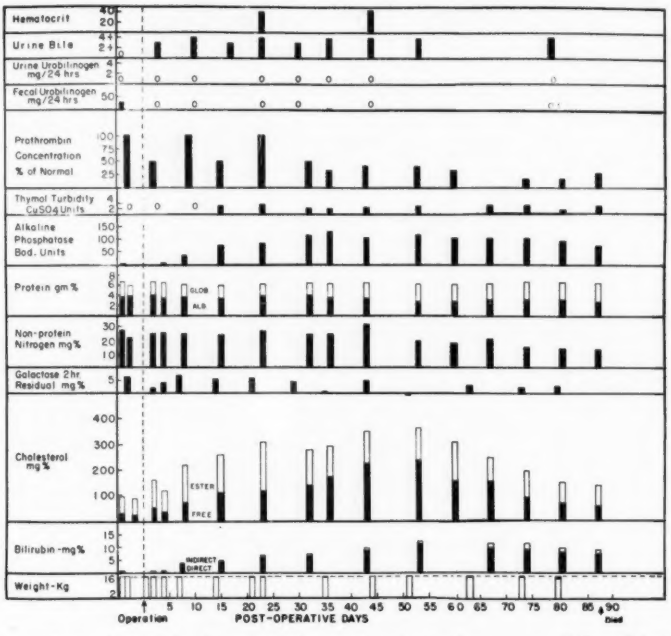

Chart 5.—Composite graph of preoperative and postoperative course of Dog M 96-52 with complete common duct obstruction.

test might become positive in simple extrahepatic obstruction. The test would thus reflect the ability of the liver to carry out at least one part of carbohydrate metabolism in the presence of obstruction.

9. Bollman, J. L.: Basic Science Notes: Army Medical Department, Research and Graduate School. Liver Function Tests, 1949, Vol. 8.

10. Zieve, L.; Manson, M., and Hill, E.: Studies of Liver Function Tests: Derivation of Correction Allowing Use of Bromsulfalein Test in Jaundiced Patents, J. Lab. & Clin. Med. **37**:40 (Jan.) 1951.

11. Colcher, H.; Patek, A. J., Jr., and Kendall, F. E.: Galactose Disappearance from Blood Stream: Calculation of Galactose Removal Constant and Its Application as a Test for Liver Function, J. Clin. Invest. **25**:768 (Sept.) 1946.

TABLE 5.—*Summary of Data on Dog MA 96-52*

Day #	Wt. Kg.	Bilirubin mg.% Dir.	Bilirubin mg.% Ind.	Cholesterol Ester mg.%	Cholesterol Ester %	Cholesterol Total mg.%	Thymol Turbidity $CuSO_4$ Units	NPN mg. %	Protein (gm.%) Total	Protein (gm.%) Alb.	Protein (gm.%) Glob.	Alk. P'tase Bod. Units	Prothrom. % conc. of normal	2 hr. Galact. resid. mg.%	Urine Bile	Urine Uro-bilin. mg/24°	Feces Uro-bilin. mg/24°
Pre-	17.3	0.12	0.36	67.5	69.1	97.5	0	29	6.54	3.73	2.81	1.1	100	6.5	0	0	28.1
Op.	17.0			67.5	74	90		23	6.02	3.84	2.18						
		Operation: Biopsy of Liver, Ligation and Division Common Duct.															
P.O.																	
2	16.2	0.6	0	110.	69	160	0	26	6.66	4.09	2.57		50	2.0			
4	16.3	0.45	0.15	85	70.9	120		27	6.49	3.51	2.98	7.2		4.0	3+	0	0
8	16.4	3.3	0.3	150	68	220	0	26	6.13	3.67	2.46	39.3	100	7.0	4+	0	0
15	16.2	4.1	0.4	150	58	260	3.0		6.18	3.28	2.90	76.1	50	5.7	4+	0	0
23	16.1	6.0	0.6	195	63	310	3.5	29	6.26	3.86	2.40	80.4	100	5.8	4+	0	0
32		6.6	0.6	140	50	280	2.0		6.35	4.11	2.24	116.3	50	4.5	4+	0	0
36	16.2			122.5	42	295	1.8		6.29	3.51	2.78	130.	33	0.3	4+	0	1.45
43	16.8	8.7	0.9	125	35.7	350	2.5	34	6.51	3.36	3.15	106.5	40	4.8			
53	16.8	11.1	0.9	127.5	35.	365	3.0	21	6.33	3.08	3.25	117.9	40	-0.5	4+	0	Trace
60				155	50	310		19	6.30	3.04	3.26	108.8	33	3.0			
67		10.2	1.2	95	38	250	3.0	22	6.31	3.14	3.17	101.0					
74	16.4	10.2	1.2	102.5	52	195	3.0	16	6.56	2.95	3.61	103.5	17	2.0			
81	15.8	8.4	1.2	77.5	52	150	1.5	15	6.61	3.15	3.46	91.0	17	2.5	4+	0	0.3
88		7.8	1.2	80	57	140	3.0	14	6.45	2.69	3.76		28				
89	Died																

Autopsy (Approximately 13 wks. post op.)

The autopsy was performed 5 days following death due to unfortunate delay. The usual details of information were unobtainable due to decomposition of the tissues. However it was noted that there was moderate emaciation, jaundice, dilatation of the biliary system, and no apparent connection between the biliary system and the intestine. Microscopic sections of the liver at autopsy revealed moderately severe biliary cirrhosis with fibrosis and bile stasis. Fat and glycogen stains were of no value because of the autolysis.

2. Method: The single-dose intravenous method using ½ gm. of galactose per kilogram body weight in a 50% solution was employed.[12] The test was first standardized on our dogs with several standard multiple point excretion curves to determine the percent error inherent in the procedure. It was found that less than 8 mg. per 100 cc. of residual galactose in the blood at the end of two hours was a normal value (Fig. 7). Accordingly, during the dogs' postoperative course the two-hour residual was used to indicate the galactose tolerance. Chemical analyses were done after the methods of Raymond and Blanco [13] and Benedict.[14] In addition, glycogen stains were made of microscopic sections of the liver at autopsy.

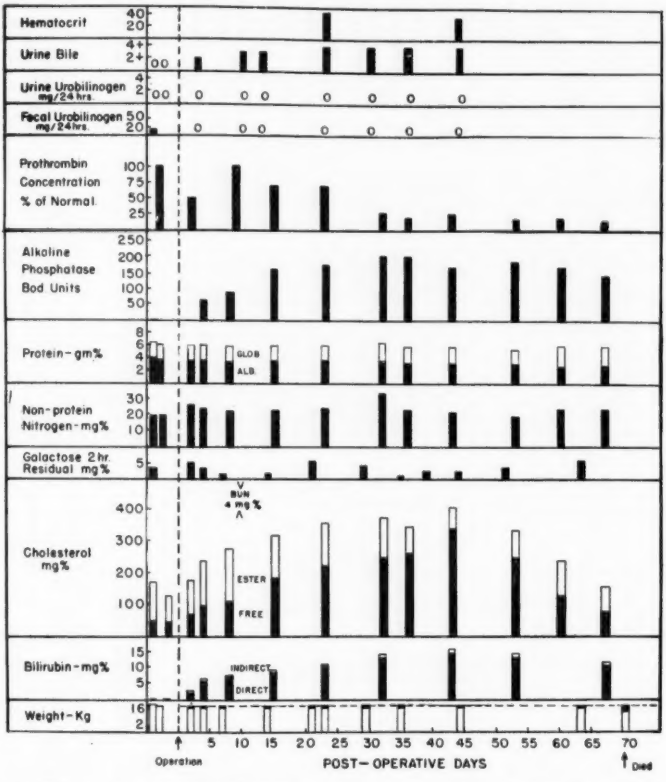

Chart 6.—Composite graph of preoperative and postoperative course of Dog CO 101-52 with complete common duct obstruction.

3. Results: Glycogen stains of sections of the liver obtained either at the time of terminal sacrifice or autopsy when compared with those made on the biopsy liver

12. King, E. J., and Aitkin, R. S.: An Intravenous Galactose-Tolerance Test, Lancet **2**:543 (Nov. 2) 1940. Colcher, Patek, and Kendall.[11]

13. Raymond, A. L., and Blanco, J. C.: Blood Sugar Determination and Separation of Sugars with Live Yeast, J. Biol. Chem. **79**:649 (Oct.) 1928.

14. Benedict, S. R.: The Determination of Blood Sugar: II., J. Biol. Chem. **76**:457 (Feb.) 1927.

TABLE 6.—*Summary of Data on Dog CO 101-52*

Day #	Wt. Kg.	Bilirubin mg.% Dir.	Bilirubin mg.% Ind.	Cholesterol Ester mg.%	Cholesterol Ester %	Cholesterol Total mg.%	Thymol Turbidity $CuSO_4$ Units	NPN mg. %	Protein (gm.%) Total	Protein (gm.%) Alb.	Protein (gm.%) Glob.	Alk. P'tase Bod. Units.	Prothrom. % conc. of normal	2 hr. Galact. resid. mg.%	Urine Bile	Urine Urobilin. mg/24°	Feces Urobilin mg/24
Pre-	17.0	0.12	0.12	125	71	175	0	20	6.50	4.18	2.32	3.2	100	3.8	0	0	13.6
Op.	16.4			85	65	130		20	6.08	3.94	2.14						
		Operation: Biopsy of Liver, Ligation and Division Common Duct															
P.O.																	
2	15.8	2.4	0.3	110	61	180	0	27	6.06	3.51	2.55		50	5.2			
4	15.2	6.0	0.6	145	60	240			6.08	3.63	2.45	63.5		3.3	2+	0	0
8	15.1	7.2	0.6	170	61	280	0	23	6.01	3.35	2.66	92.8	100	1.2	3+	0	Trace
15	15.2	8.7	1.2	135	42	320	4.0		6.24	3.58	2.66	164.1	70	1.5	3+	0	Trace
23	15.3	10.5	0.9	140	39	360	7.5	25	6.33	3.57	2.76	179.1	70	5.5	4+	0	0
32	15.3	13.2	1.2	130	34	380	3.5	34	6.45	3.64	2.81	217.4	28	4.3	4+	0	0
36	15.1			87	25	350	4.0	23	5.77	3.18	2.59	216.4	20	0.8	4+	0	Trace
43	15.3	14.4	1.8	70	17	410	5.5	22	5.80	3.20	2.60	171.4	25	2.5	4+	0	0
53		13.2	1.2	85	25.4	335	6.0	19	5.39	3.13	2.26	199.3	18	4.0			
60	15.1			110	46	240		24	6.04	2.76	3.28	170.3	18				
67	13.7	11.1	0.9	80	50	160	2.5	24	6.00	2.88	3.12	144.1	15	6.0			
70	Died																

Autopsy (10 weeks post operation)

Animal thin, emaciated and jaundiced. Weight 13.7 kg. Very little subcutaneous fat. There were 350-400 c.c. of bile-stained fluid in the peritoneal cavity, but no evidence of peritonitis. All organs including the bowel surface showed yellow discoloration. Liver enlarged, greenish-brown, firm, smooth and had a sharp edge. Weight 750 grams. Gall bladder and common duct marked enlarged. No connection with intestinal tract. Contents of small intestine colorless. Spleen enlarged, weight 110 grams. Lungs and heart normal. Kidneys normal, 86 and 90 grams. Colon contained small amount of pale formed feces.

Microscopic examination of the liver showed moderately severe biliary cirrhosis with the usual fibrosis and bile stasis. Fat and glycogen stains were not of value because there was a delay of several hours after death before the autopsy was performed.

specimens obtained at operation showed only a slight to moderate decrease in gross content. The intravenous galactose tolerance test showed no significant evidence of impairment throughout the duration of the dogs' postoperative period (Figs. 4 to 6; Tables 4 to 6). The test was performed in all animals, but, unfortunately, it was learned after completion of the first three tests that we were being supplied with oxylate blood sample tubes containing fluoride. Since this interfered to varying degrees with the fermentation of the glucose by the yeast, our results in these three dogs were not significant and therefore discarded. The remaining three dogs show satisfactorily the lack of impairment in this function, even after a period of 17 weeks, as in the case of Dog KI 24-25 (Chart 4; Table 4).

4. Comment: The persistently normal intravenous galactose tests and the slight to moderate liver glycogen depletion by microscopic examination at autopsy suggest that the liver is probably able to metabolize carbohydrates in the presence of simple

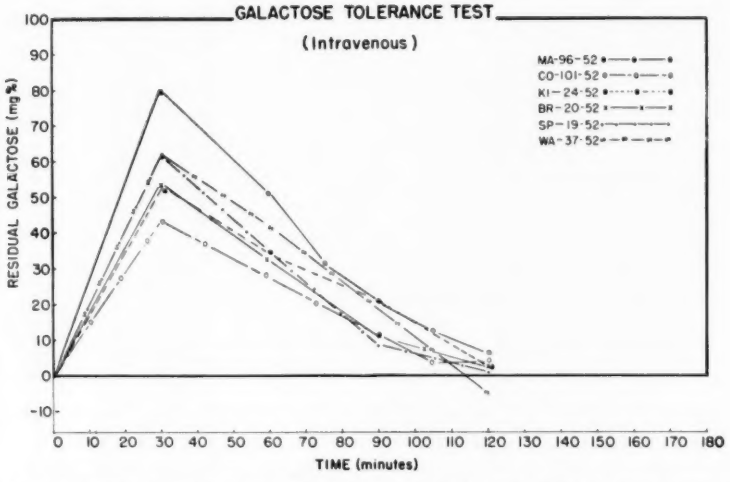

Chart 7.—Graphic result of intravenous galactose tolerance test (0.5 gm. galactose per kilogram body weight) performed in six normal dogs.

obstruction rather well but that the caloric requirements and the decreased availability of fat as a nutrient result in increased glycogenolysis.

III. *Fat Metabolism.*—1. Historical Background: Johnson, Ravdin, Vars, and Zintel,[15] working with dogs, found in analyzing the liver at autopsy (performed from 13 to 35 days following obstruction of the common duct) that there was an average of 21.9 gm. per 100 cc. of fatty acids, as contrasted with their control normal average of 9.8 gm. per 100 cc. Searle and Annegers[16] have studied the

15. Johnson, J.; Ravdin, I. S.; Vars, H. M., and Zintel, H. A.: Symposium on Preoperative and Postoperative Treatment: Effect of Diet on Composition of the Liver in the Presence of Obstruction of the Common Duct, Arch. Surg. **40**:1104 (June) 1940.

16. Searle, G. W., and Annegers, J. H.: Correction of Steatorrhea in Bile Fistula Dogs by Frequent Return of Bile, Proc. Soc. Exper. Biol. & Med. **71**:277 (June) 1949; Correction of Steatorrhea in Bile Fistula Dogs by Duodenal and Oral Administration of Bile Substitutes, Gastroenterology **19**:558 (Nov.) 1951.

steatorrhea that occurs in dogs with diversion of bile by fistula and in addition have shown the value of bile substitutes in correcting this. The alterations in cholesterol metabolism following obstruction of the common duct have had considerable study both clinically and experimentally. Byers, Friedman, and Michaels,[17] working with rats, have shown that after ligation of the common bile duct there is a marked increase in the cholesterol content of the plasma. This increase consisted largely of free cholesterol. Hawkins and Wright [18] studied the fluctuation in plasma cholesterol in four dogs following obstruction of the common duct. Over a period of 27 days following operation they noted that both total and esterified cholesterol increased definitely above control levels but that there was no significant change in the ratio of ester to total cholesterol. At the end of this period of observation they then gave the dogs frequent doses of chloroform to further injure the liver and noted a rapid fall in total cholesterol but even more so in the ester. During the last two days of life in these dogs there were no cholesterol esters demonstrated in the blood.

There are a number of clinical reports concerning the changes found in the plasma cholesterol in patients with biliary obstruction. There is general agreement that the total cholesterol usually rises early in the course of obstruction. Epstein and Greenspan [19] found that there was a more marked hypercholesteremia in cases with complete obstruction (i. e., carcinoma of pancreas) than in cases with obstruction due to calculi. Reports differ as to the course of the ester and free fractions. Epstein and Greenspan found the cholesterol ester above normal in 75% of 105 cases of obstructive jaundice and either normal or low in their cases of acute hepatic disease. Jones [20] noted in a study of 19 patients with obstructive jaundice that there was more regularly an increase in free cholesterol than in either the total cholesterol or the ester. Ricketts and Sterling [20] in a study of 48 cases of biliary cirrhosis noted a consistent elevation in total cholesterol. The variation in findings undoubtedly depends upon the selection of cases. Few cases of obstruction in the human being are free of complicating factors such as ascending infection, intermittent obstruction, incomplete obstruction, and associated hepatocellular disease.

There is apparently little information on the changes in the cholesterol fractions in the terminal stages of obstructive jaundice in controlled experiments.

2. Method: The serum cholesterol, both free and total, was determined by using the revised Schoenheimer-Sperry method of 1950.[21] In addition, fat stains were made of the microscopic sections of the liver at autopsy.

3. Results: In all cases there was an abrupt rise in the level of total serum cholesterol. This rise was apparent as early as two days following operation. This

17. Byers, S. O.; Friedman, M., and Michaels, F.: Observations Concerning Production and Excretion of Cholesterol in Mammals: III. Source of Excess Plasma Cholesterol after Ligation of Bile Duct. J. Biol. Chem. **188**:637 (Feb.) 1951.

18. Hawkins, W. B., and Wright, A.: III. Blood Plasma Cholesterol: Fluctuations Due to Liver Injury and Bile Duct Obstructions, J. Exper. Med. **59**:427 (April) 1934.

19. Epstein, E. Z., and Greenspan, E. B.: Clinical Significance of the Cholesterol Partition of the Blood Plasma in Hepatic and in Biliary Diseases, Arch. Int. Med. **58**:860 (Nov.) 1936.

20. Jones, C. A.: Clinical and Laboratory Study of Plasma Lipids in Obstructive Jaundice and Several Types of Hepatic Disease, Am. J. Digest. Dis. **9**:1 (Jan.) 1942.

21. Sperry, W. M., and Webb, M.: A Revision of the Schoenheimer-Sperry Method for Cholesterol Determination, J. Biol. Chem. **187**:97 (Nov.) 1950.

level then remained elevated for periods of time which varied from dog to dog. The level in the two dogs (Figs. 1 and 2; Tables 1 and 2) that lived but six and seven weeks, respectively, after operation showed a return to preoperative levels in about three weeks. The levels in the remaining four dogs (Charts 3 and 6; Tables 3 and 6) remained above preoperative levels for periods ranging from 6 to 11 weeks. In two of the animals (Charts 3 and 4; Tables 3 and 4), both of which lived longer than two months, the level of total serum cholesterol eventually fell to levels significantly lower than the preoperative levels. Both these animals showed a profound loss of weight and at autopsy showed extreme emaciation, remarkable diminution of the amount of fat in the usual fat deposits (i. e., subcutaneous tissues, mesentery, and omentum), and moderate to extensive fatty infiltration of the liver. The course of the percent of cholesterol esterified by the liver was also of interest. Four dogs (Charts 1, 3, 5 and 6; Tables 1, 3, 5, and 6) showed that the percent of ester progressively decreased as the level of total cholesterol remained elevated, and then, as the level of total cholesterol fell terminally, the percent of ester rose somewhat. One dog (Chart 2; Table 2) showed a relentless fall in the percent of ester throughout the postoperative course. The remaining dog (Chart 3; Table 3) showed no striking change in the percent of ester, although the level of the total cholesterol followed the typical course of an abrupt rise and late fall.

In contrast with the course of the percent of ester, the actual amount of ester followed a consistent pattern. In all cases there was an early significant rise in the level of ester, which persisted from three to five weeks, and then a gradual fall, which in four dogs fell well below normal (Charts 1 and 4; Tables 1 and 4). In the other two dogs this fell only to preoperative levels (Charts 5 and 6; Tables 5 and 6).

Thus in all cases there was an early rise in the levels of both cholesterol ester and total cholesterol.

In addition to the studies of the cholesterol pattern the microscopic examination of the liver at autopsy with fat stains showed a moderate degree of fatty infiltration.

4. Comment: The marked weight loss, the striking decrease in the amount of subcutaneous fat found at autopsy, the moderate fatty infiltration in the liver at autopsy, and the eventual fall of the level of total cholesterol and cholesterol ester in this study reflect the extreme changes in fat metabolism in the presence of complete biliary obstruction. The changes noted in the total and esterified cholesterol are of considerable interest. It is apparent that common duct obstruction consistently results in hypercholesteremia, whether directly or indirectly. Byers, Friedman, and Michaels [17] have reported evidence from their studies with rats to indicate that cholesterol is formed by the liver. They have also concluded from additional work that [22] the accumulation of bile acid occurring in the plasma after biliary obstruction in the rat appears to be responsible for the hypercholesteremia. If this is true, then the terminal fall in the level of serum total cholesterol merely reflects the terminal fall in the level of serum bile acids, as noted by Snell and his associates,[23]

22. Friedman, M., and Byers, S. O.: Production and Excretion of Cholesterol in Mammals: VI. Bile Acid Accumulation in Production of Hypercholestermia Occurring after Biliary Obstruction, Am. J. Physiol. **168**:292 (Feb.) 1952.

23. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Diseases of the Liver: VII. Further Studies in Experimental Obstructive Jaundice, Arch. Int. Med. **40**:471 (Oct.) 1927. Snell, Greene, and Rountree.[7]

rather than actual impairment in the ability of the liver cell to produce cholesterol and in turn to esterify it. This would not seem to be the only explanation, since Hawkins and Wright [18] have noted the complete disappearance of plasma cholesterol esters in dogs receiving chloroform after 27 days of complete biliary obstruction. So far as there was still free cholesterol remaining in the serum, their data would suggest impairment of the ability of the liver cell to esterify cholesterol. Thus the gradual fall in the level of the serum cholesterol ester following the initial postoperative elevation observed in the present experiments would seem to reflect impairment of liver cell function. It would also seem possible that in spite of the evidence to suggest that bile-acid retention is responsible for the hypercholesteremia in biliary obstruction, the gradual fall in the total serum cholesterol may reflect impairment in the ability of the liver cell to produce cholesterol. That this terminal fall is not a reflection of impaired gastrointestinal absorption has been shown by Friedman and Byers.[22] That this is probably not a reflection of starvation is suggested by the observation of Kartin and his associates,[24] who found that there were no consistent changes in the serum lipids of dogs during starvation. These data are not conclusive evidence, since their observations covered periods of but 4 to 14 days. It seems apparent that in the presence of biliary obstruction the dog uses the depot fats of his body as an important source of calories. It would therefore be of interest to know to what extent oral bile therapy would alter the changes noted previously.

IV. *Serum Alkaline Phosphatase.*—1. Historical Background: Within the past few years there has been considerable study of the serum alkaline phosphatase in relation to biliary obstruction. Its value as an aid in the differential diagnosis of hepatocellular jaundice and obstructive jaundice was quickly appreciated. MacLagan,[25] in 1947, reviewed 200 cases and found that the combination of the serum alkaline phosphatase determination and one flocculation test would distinguish obstructive from nonobstructive jaundice in from 65 to 79% of cases. Tanturi and his associates [26] and Dalgaard [27] working with dogs and cats, respectively, have reported that after obstruction of the common duct there is an early rise in the serum alkaline phosphatase level, which remains elevated for considerable time and then gradually falls. The falling level, however, never reaches normal.

Wang and Grossman [28] and Freeman [29] have submitted important evidence to indicate that the elevated serum alkaline phosphatase level noted in obstructive jaundice is actually produced by the liver.

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24. Kartin, B. L.; Man, E. B.; Winkler, A. W., and Peters, J. P.: Blood Ketones and Serum Lipids in Starvation and Water Deprivation, J. Clin. Invest. **23**:824 (Sept.) 1944.

25. MacLagan, N. F.: Liver Function Tests in the Diagnosis of Jaundice: Review of 200 Cases, Brit. M. J. **2**:197 (Aug. 9) 1947.

26. Tanturi, C. A.; Canepa, J. F.; Bay, R., and Banfi, R. F.: Experimental Study on Liver Function Tests. Surg. Gynec. & Obst. **83**:171 (Aug.) 1946.

27. Dalgaard, J. B.: Phosphatase in Cats with Obstructive Jaundice, Acta physiol. scandinav. **15**:290, 1948.

28. Wang, C. C., and Grossman, M. I.: Non-Excretion of Serum Alkaline Phosphatase by the Liver and the Pancreas of Normal Dogs, Am. J. Physiol. **156**:256 (Feb.) 1949.

29. Freeman, S.: Comparison of Effects of Hepatectomy and of Common Bile Duct Obstruction on Serum Phosphatase of Adult Dogs, Am. J. Physiol. **164**:792 (March) 1951.

2. Method: Serum alkaline phosphatase determinations were done by the method of Bodansky.[30]

3. Results: In all cases the serum alkaline phosphatase followed a consistent pattern. From preoperative levels ranging between 0 and 3.2 Bodansky units the level rose abruptly immediately after operation. A significant elevation was apparent by the second postoperative day. The levels then continued to rise to levels frequently over 200 units. Most of the animals showed the greatest rise within the first eight days, but the rise continued for three to five weeks. All but one dog showed a late fall in the level. This fall, however, never reached a level under 50 Bodansky units. The one dog which failed to show this fall may well have had it, since alkaline phosphatase determinations were not done in the terminal part of the postoperative course (Chart 1; Table 1). It should be emphasized that the alkaline phosphatase pattern failed to show a single deviation from the basic pattern of abrupt and significant postoperative elevation.

4. Comment: The consistent pattern in the abrupt postoperative rise in the serum alkaline phosphatase and the persistence of this level well above normal limits lend significance to the value of this determination in indicating obstruction. The late fall in the level, which, however, never reached normal, reflects impairment of liver cell ability to secrete the enzyme.

V. *Serum Bilirubin, Fecal Urobilinogen, Urine Bile, and Urine Urobilinogen.*—1. Historical Background: Clinically, Sherlock [1] in following six cases of unrelieved common duct obstruction in human beings found that the level of serum bilirubin rose steadily for the first three weeks of jaundice and then fluctuated, the trend being upward. Snell, Green, and Rowntree [23] in their work with dogs found in the average case that the level reached a peak of approximately 9 mg. per 100 cc. within two weeks following obstruction of the common duct and then during the ensuing several weeks gradually fell to a plateau. This was also noted by Carr and Foote [31] and by Tanturi and his associates [26] in dogs, and by Edlund [6] in rats. Robscheit-Robbins and Whipple [32] have submitted evidence to indicate that the eventual fall in the serum bilirubin level is based on a decrease in the formation of parent substances for hemoglobin by the liver itself.

2. Method: Serum bilirubin determinations, both direct and total, were done by the method of Malloy and Evelyn.[33] Twenty-four hour fecal urobilinogen excretion studies were performed by the method of Watson.[34] Stool specimens were for the most part collected over a four-day period upon which to base the 24-hour excretion. Only guaiac-negative specimens were recorded. Twenty-four hour urine

30. Bodansky, A.: Determination of Serum Inorganic Phosphate and Serum Phosphatase Activity, Am. J. Clin. Path. (Technical section) **7**:51, (Sept.) 1937.

31. Carr, J. L., and Foote, F. S.: Progressive Obstructive Jaundice: Changes in Certain Elements of Blood and Their Relation to Coagulation, Arch. Surg. **29**:277 (Aug.) 1934.

32. Robscheit-Robbins, F. S., and Whipple, G. H.: Hemoglobin Production Factors in the Human Liver: II. Liver Degeneration, Cancer, Cirrhosis and Hepatic Insufficiency, J. Exper. Med. **57**:653 (April) 1933.

33. Malloy, H. T., and Evelyn, K. A.: Determination of Bilirubin with the Photo-Electric Colorimeter, J. Biol. Chem. **119**:481 (July) 1937.

34. Watson, C. J.: Studies of Urobilinogen: I. Improved Method for Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458 (Sept.) 1936.

urobilinogen excretion studies were also performed by the method of Watson.[34] The presence of bilirubin in the urine was determined grossly by the Harrison spot test [35] on the basis of 0 to 4+.

3. Results: All but one animal (Fig. 2; Table 2) showed an early rise in serum bilirubin, followed by more or less of a plateau, and then a late slight fall. With the exception of this same dog (Fig. 2, Table 2) the level of total bilirubin never exceeded 15 mg./100 cc. Normally the dog has little or no bilirubin in the serum detectable by the usual methods. This was found to be true in our preoperative determinations. The serum was grossly colorless. A significant increase was noted by the second postoperative day. In all animals throughout their postoperative course the determinations invariably showed an overwhelming percent of direct-reacting bilirubin. It was thought initially that with progressive failure of the liver as a whole and with the concept that indirect bilirubin is converted to direct bilirubin by the liver cell, that one would expect to find an increasing percent of indirect bilirubin as the postoperative course progressed. This was not observed.

Bile appeared in the urine by the fourth postoperative day and was present in large concentration until death.

Another route of excretion of bilirubin, although admittedly very small, was found to be the wall of the large intestine. Most of the stools were found to consist of a large central slate-gray core and a thin exterior of dark-brown feces. Quantitative 24-hour fecal urobilinogen determinations throughout the postoperative course frequently showed small amounts of urobilinogen. Each of the six autopsies confirmed the completeness of the obstruction and the absence of any possible connection between the divided ends of the common duct or between the proximal end and the intestine. Since small amounts of urobilinogen were often present in the feces, it is thus reasonable to expect reabsorption and excretion in the urine, since it cannot be reexcreted by the liver. With respect to the results of the microscopic study of the sections of liver taken at autopsy, there was the expected evidence of typical biliary cirrhosis to a varying degree, depending upon the duration of the postoperative course. In all cases, however, the liver grossly was found to have a smooth, although enlarged, surface.

4. Comment: The postoperative course of the serum total bilirubin in the cases showing the early rise and terminal fall to levels still above normal reflected eventual impairment of liver function. The suggestion by Robscheit-Robbins and Whipple [32] that the decrease is based on impaired production of parent substances of hemoglobin by the liver would seem more reasonable than impairment of the excretory ability of the liver. And if we accept the theory that the direct-reacting serum bilirubin is regurgitated or regains the vascular system via the lymphatics after having been separated from its protein attachment by the liver cell, then the consistently small level of indirect-reacting serum bilirubin indicates no impairment of excretory ability. This is somewhat of a surprise, since Jankelson and Gargill [36] and Weech and his associates [37] have shown that the ability of the liver to excrete bilirubin is

35. Ford, A. G., and Baisinger, C. F.: Comparison of Tests for Bilirubin in Urine, Am. J. Clin. Path. **10**:238 (March) 1940.

36. Jankelson, I. R., and Gargill, S. L.: Bilirubin Liver Function Test, New England J. M. **204**:547 (March 12) 1931.

37. Weech, A. A.; Vann, D., and Grillo, R. A.: The Clearance of Bilirubin from the Plasma: A Measure of the Excretory Power of the Liver, J. Clin. Invest. **20**:323 (May) 1941.

one of its most sensitive functions. One would expect a terminal rise in the serum bilirubin as the excretory ability of the liver became impaired. This occurred in only one of the animals (Chart 2; Table 2). The fact that the level of indirect bilirubin remains small even in such circumstances suggests that the two functions (i. e., excretion and conversion of indirect bilirubin to direct bilirubin) are carried on by different units in the liver or even that the conversion of indirect to direct is indeed not a function of excretion by the liver. This latter possibility has been the subject of critical investigation in 1950 by Klatskin and Drill,[38] who report evidence suggesting that the rate of diazotization is determined by the concentration and by chemical or physical factors in the serum.

Autopsy examination and the determination of urobilinogen in the feces and urine gave satisfactory evidence that the common duct obstruction was complete in all the dogs. The small traces of urobilinogen in the feces on occasions in the postoperative course, together with the observation that the stool specimens often consisted of a central slate-gray core covered with a thin exterior of brown feces; the colorless contents of the small intestine, and negative spot checks for urobilinogen and bilirubin in the food strongly suggest that in the dog bilirubin does transgress the wall of the colon. Furthermore, the small traces of urobilinogen found in the urine on occasions could be accounted for on this basis. Of interest in this matter is the experience of Burnett,[39] who has observed that dogs with a biliary fistula by means of a choledochoureterostomy also show traces of urobilinogen in the feces. It is his feeling that in such cases the source must be dietary. The architecture of the stool specimen, however, would indicate that the source of the fecal urobilinogen in the present experiments is from bilirubin which transgresses the colon wall and is then in turn converted to urobilinogen by the bacteria.

VI. *Plasma Prothrombin.*—1. Historical Background: The discovery of the relation of prothrombin deficiency to hemorrhage in the jaundiced patient is one of the highlights in the progress of biliary surgery. Hawkins and Brinkhaus [40] in 1936 showed that whole bile both prevented and cured prothrombin deficiency in dogs with biliary fistulas.

Several authors [41] have noted that several weeks, even a few months, could elapse before any hemorrhagic tendency could be noted. Quick [41c] observed that in infants with biliary atresia it is not uncommon to find only a mild hypoprothrombinemia even after many months. One of the most significant reports is that of Lord, Andrus, and Moore,[41a] who, in 1940, working with dogs, showed that vitamin K is stored in the liver after absorption from the intestine and that after common duct obstruction there is a linear fall in the level of plasma prothrombin. They also showed that it often took as long as 105 to 160 days following operation

38. Klatskin, G., and Drill, V. A.: The Significance of the "One-Minute" (Prompt Direct Reacting) Bilirubin in Serum, J. Clin. Invest. **29**:660 (June) 1950.

39. Burnett, W.: Personal communication to the author.

40. Hawkins, W. B., and Brinkhaus, K. M.: Prothrombin Deficiency: The Cause of Bleeding in Bile Fistula Dogs, J. Exper. Med. **63**:795 (June) 1936.

41. (*a*) Lord, J. W.; Andrus, W. D., and Moore, R. A.: Metabolism of Vitamin K and Role of Liver in the Production of Prothrombin in Animals, Arch Surg. **41**:585 (Sept.) 1940. (*b*) Smith, H. P.; Warner, E. D.; Brinkhaus, K .M., and Seegers, W. H.: Bleeding Tendency and Prothrombin Deficiency in Biliary Fistula Dogs: Effect of Feeding Bile and Vitamin K, J. Exper. Med. **67**:911 (June) 1938. (*c*) Quick, A. J.: Personal communication to the author. (*d*) Tanturi and others.[26]

to reach a hemorrhagic level. The hemorrhagic level in dogs varies from 10 to 20% of normal. In sharp contrast with this is their observation that after hepatectomy the prothrombin level fell to hemorrhagic levels within 10 hours. And since it is necessary to have a normal concentration of fibrinogen present for accurate prothromin determinations, it is of importance to note that Moss,[42] in 1933, observed that the concentration of fibrinogen is increased in obstructive jaundice in dogs. Recent electrophoretic analyses [43] of serum and plasma proteins of patients with obstructive jaundice support the findings of Moss.

2. Method: Prothrombin plasma levels, percent concentration of normal, were determined by using the modification of the Quick test, as described by Aggeler and his associates.[44] A standard curve was obtained by serial dilutions of dog plasma, using prothrombin free plasma as a diluent. Human brain served as our source of thromboplastin. Periodic determinations were transposed to percent concentration of normal from the standard curve. Dilution of the individual specimen with prothrombin-free plasma in order to benefit from the more accurate part of the curve was not done, although this undoubtedly would have given more detailed information. In spite of this the results yielded satisfactory and significant information.

3. Results: After operation the plasma prothrombin did not reach hemorrhagic levels in any case. However, there was a progressive fall in the level, which, from a preoperative level of 100% concentration of normal, reached a level of 20% or lower in four animals.

4. Comment: The observations on the progressive levels of plasma prothrombin concentration in the postoperative course merely confirm the observations of others [41a] that there is a progressive fall and that in dogs death usually occurs in complete biliary obstruction before hemorrhagic levels are reached. From this experiment it would seem impossible to relate the changes observed to impaired ability of the liver cell to convert vitamin K to prothrombin, since absorption of vitamin K depends upon the presence of bile salts. It would be of interest to test the capacity of the cell to carry out this function in various stages of the postoperative course by the parenteral administration of vitamin K.

VII. *Thymol Turbidity.*—1. Historical Background: Since the thymol turbidity test was introduced in 1944 by MacLagan,[45] it has rapidly gained well-deserved popularity. At first based upon empirical observations of its association with hepatocellular disease, evidence by means of electrophoretic serum protein studies now indicates that it is most probably associated with the elevation of the

42. Moss, W.: Experimental Obstructive Jaundice: Its Effect on Fibrinogen and Coagulation of Blood, Arch. Surg. **26**:1 (Jan.) 1933.

43. Franklin, M.; Bean, W. B.; Paul, W. D.; Routh, J. I.; Huerga, J. de la, and Popper, H.: Electrophoretic Studies in Liver Disease: I. Comparison of Serum and Plasma Electrophoretic Patterns in Liver Disease with Special Reference to Fibrinogen and Gamma Globulin Patterns, Clin. Invest. **30**:718 (July) 1951. Franklin and others.[2a]

44. Aggeler, P. M.; Howard, J.; Lucia, S. P.; Clark, W. and Astaff, A.: Standardization of the Quick Prothrombin Test, with Reference to the Statistical Significance of Variations in the Prothrombin Use of a Stable Thromboplastin of High Potency, Blood **1**:220 (May) 1946.

45. MacLagan, N. F.: Thymol Turbidity Test: A New Indicator of Liver Dysfunction, Nature **154**:670 (Nov. 25) 1944.

gamma globulin.[46] Considerable clinical experience has accumulated [47] to indicate the value of the test, both in the differential diagnosis of jaundice and as an aid in following the course of a patient with hepatitis. In man its elevation in the presence of obstructive jaundice is considered to indicate secondary hepatocellular disease. Little study of the test has apparently been done in the experimental animal. Gornall and Bardawill [48] in their study of 25 dogs over a period of three years in which they studied the effects of carbon tetrachloride poisoning found that the thymol test reflected hepatocellular disease satisfactorily but not as accurately as in human beings. Edlund [6] working with rats with complete biliary obstruction found no changes from the normal throughout the postoperative course.

2. Method: Thymol turbidity determinations were performed by Ducci's modification of the method of MacLagan.[49] Results are stated in terms of units with a normal range of 2 to 4.

3. Results: The thymol turbidity, selected to indicate inflammatory hepatocellular disease, remained within normal limits throughout the entire postoperative course in all dogs. Microscopic sections of the liver at autopsy in four of the dogs confirmed the absence of any inflammation.

4. Comment: The consistently normal thymol turbidity determinations and the absence of evidence of acute inflammation in the liver by microscopic examination at autopsy confirmed the impression that this has been a study of simple mechanical biliary obstruction. They also indicate that the effects noted are those due to simple obstruction alone.

VIII. *Weight.*—All of the dogs showed progressive loss of weight and eventual emaciation. At autopsy in each case the loss of subcutaneous fat was quite striking. The actual loss of weight varied in degree. Some of the dogs lost nearly half of their preoperative body weight. This was only in small part due to insufficient dietary intake, since in the case of Dog KI 24-52 the daily portion of food offered was completely consumed until the last two days of his postoperative course. The weight loss and emaciation in this case were remarkable, as will be seen in Figure 4 and Table 4. In some of the other dogs poor dietary intake undoubtedly played a role. However, it is quite apparent that with the complete loss of bile acids in the small intestine the absorption of fats will be markedly decreased, and, consequently, a major source of calories will be lost. This then accounts for the striking decrease in the amount of fat in the fat depots, such as the subcutaneous tissue and mesentery. One might expect in these circumstances of increased oxidation of the

46. MacLagan, N. F., and Bunn, D.: Flocculation Tests with Electrophoretically Separated Serum Proteins, Biochem. J. **41**:580 (Oct.) 1947.

47. Watson, C. J., and Rappaport, E. M.: A Comparison of the Results Obtained with the Hanger Cephaline Cholesterol Flocculation Test and the MacLagan Thymol Turbidity Test in Patients with Liver Disease, J. Lab. & Clin. Med. **30**:983 (Dec.) 1945. Meyer, K. A., and Popper, H.: Laboratory Diagnosis and Its Pitfalls in the Management of Surgical Jaundice, S. Clin. North America **27**:37 (Feb.) 1947. MacLagan, N. F.: The Thymol Turbidity Test as an Indicator of Liver Dysfunction, Brit. J. Exper. Path. **25**:234 (Dec.) 1944. Bollman.[9] Zieve, Manson, and Hill.[10]

48. Gornall, A. G., and Bardawill, C. J.: Study of Liver Function in Dogs, Canad. J. M. Sc. **30**:256 (June) 1952.

49. Ducci, H.: Thymol Test of MacLagan: Standardization and Adaptation to Evelyn Photoelectric Colorimeter, J. Lab. & Clin. Med. **32**:1266 (Oct.) 1947.

fat in the depots that one would find a high level of acetone bodies in the urine.[24] Several determinations for acetone in the urine were negative.

SUMMARY

The nature of liver failure due to simple complete biliary obstruction has been described in a series of six dogs.

Evidence of impairment of liver function lies in the following observations:

A. There was a progressive fall in the level of the serum albumin and a rise in the globulin.

B. After the initial abrupt postoperative rise in the level of serum alkaline phosphatase there was a gradual fall. This fall did not, however, reach preoperative values.

C. After the initial postoperative rise in the levels of serum total cholesterol and cholesterol ester, which persisted for a few weeks, there was an eventual fall. In the majority of cases the cholesterol ester level eventually fell below the preoperative value.

D. After the initial rise there was eventually a gradual fall in the level of serum bilirubin.

Emaciation was a striking feature in the postoperative course in spite of adequate dietary intake.

There was no impairment in the ability of the liver to metabolize galactose although there was a moderate decrease in liver glycogen at autopsy.

There was a gradual decrease in the plasma prothrombin concentration which did not reach hemorrhagic levels.

There was no change noted in the thymol turbidity test in any of the animals.

Death is apparently due to combined liver failure and emaciation.

145 Kearney St.

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INDICATIONS FOR LIGATION OF THE INFERIOR VENA CAVA IN VENOUS THROMBOSIS

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THE RELATIONSHIP of phlebitis of the lower limbs to pulmonary embolus was established by Virchow in 1846-1856.[1] Since that time much has been learned about the incidence of phlebitis and the statistical relationship of the various types of phlebitis to pulmonary embolism. However, the serious problem of preventing emboli from reaching the lungs has not been satisfactorily solved to date. As a corollary of this, the prevention of further emboli after the initial one has reached the lungs is also a serious problem. It is with these two problems that this paper is concerned.

The treatment of thrombophlebitis complicated by pulmonary emboli has gone through three general eras which have been marked by waves of enthusiasm, unpopularity, and final acceptance for a definite set of clinical circumstances. The concept of venous interruption was proposed in 1934.[2] This has since been applied to all levels in the lower extremities, the anatomical level ascending with the accumulation of information and courage on the part of the surgeon. The most satisfactory level for therapeutic interruption was found to be distal to the profunda femoris, and this ligation was used as a routine procedure for thrombophlebitis unattended by emboli or symptoms. The prophylactic ligation prior to major surgery was found to have statistical validity as a procedure.[3] However, repeated instances were reported of pulmonary emboli occurring after a bilateral ligation distal to the profunda femoris.[4] It was then proposed that the venous interruption

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1. Welch, W. H.: Papers and Addresses: Embolism, Baltimore, The Johns Hopkins Press, 1920, Vol. 1, pp. 193-258.

2. (*a*) Homans, J.: Thrombosis of the Deep Veins of the Lower Leg, Causing Pulmonary Embolsm, New England J. Med. **211**:993-997 (Nov. 29) 1934. (*b*) Homans, J.: Deep Quiet Venous Thrombosis in the Lower Limb: Preferred Levels for Interruption of Veins; Iliac Sector or Ligation, Surg., Gynec. & Obst. **79**:70-82 (July) 1944.

3. Allen, A. W.: Management of Thromboembolic Disease in Surgical Patients, Surg., Gynec. & Obst. **96**:107-114 (Jan.) 1953.

4. (*a*) Veal, J. R.; Hussey, H. H., and Barnes, E.: Ligation of the Inferior Vena Cava in Thrombosis of the Deep Veins of the Lower Extremities, Surg., Gynec. & Obst. **84**:605-610 (April) 1947. (*b*) Thebaut, B. R., and Ward, C. S.: Ligation of the Inferior Vena Cava in Thromboembolism: Report of 36 Cases, ibid. **84**:385-401 (April) 1947.

be at the level of the common iliac or the lower inferior vena cava. This level of ligation was used by several groups with varying success. The incidence of disability was a factor in preventing ligation at this level from achieving universal use.[2b]

The development of anticoagulants into more usable forms led to their application in the treatment of thrombophlebitis and thromboembolic disease. Heparinization was found to be a practicable kind of treatment; however, the certainty of results, even in the best hands, was dependent on many details.[5] The further perfection of longer-acting heparin compounds, together with a better understanding of individual reactions to such substances, has made heparinization an increasingly popular technique in the treatment of thrombophlebitis. Some prefer heparinization to the exclusion of all other forms of therapy for the uncomplicated phlebitis.

Coincident with the development of heparin as an anticoagulant, the longer-acting bishydroxycoumarin (Dicumarol) type of anticoagulants were developed.

TABLE 1.—*Indications Proposed for Ligation of the Inferior Vena Cava*

Northway and Buxton [3a]	
	Trauma (accidental or coincident with surgery)
	Puerperal pyemia
	Quiet thrombosis of lower extremities
	Bilateral ascending thrombosis
	Silent thrombosis
Kirk [3b]	
	To localize infection of the lower extremities
Carpenter and Dibble [3c]	
	Femoroiliac thrombophlebitis with emboli
Newman,[3d] Collins, MacCallum, Nelson, Weinstein, and Collins [3e]	
	Parametritis with pelvic thrombophlebitis and pulmonary emboli
O'Neil [3f]	
	One or more pulmonary emboli when source is obscure
	Concurrent phlebothrombosis in both legs, above the inguinal ligament in one leg
Oaks and Hawthorne [3g]	
	Pseudoembolic phlebitis (phlegmasia caerulia dolens of Gregoire)
Veal, Hussey, and Barnes [4a]	
	Ascending thrombosis of the lower extremities above the inguinal ligament and with pulmonary embolism

The application of these drugs to thrombophlebitis has been popular because of the ease of administration and the lower cost as compared with heparinization. The incidence of complications and the difficulty to control have led many to discard bishydroxycoumarin, but other similar substances have been developed which may eliminate these objections.[6]

At present many observers feel [5] that the treatment of thrombophlebitis of any type is best done with anticoagulants. The difficulty arises when a pulmonary embolus occurs. In these circumstances some sort of interruption of the venous system seems to be the best means of preventing another and perhaps a fatal embolus

5. (*a*) Duff, I. F.; Linman, J. W., and Birch, R.: The Administration of Heparin, Surg., Gynec. & Obst. **93**:343-362 (Sept.) 1951. (*b*) Marple, C. D., and Wright, I. S.: Thromboembolic Conditions and Their Treatment with Anticoagulants, Springfield, Ill., Charles C Thomas, Publisher, 1950.

6. Burke, G. E., and Wright, I. S.: Tromexan—3,3′-Carboxymethylenebis (4-Hydroxycoumarin) Ethyl Ester: Experimental and Clinical Properties, Circulation **3**:164-170 (Feb.) 1951.

from reaching the lungs. The level of this interruption ideally should be proximal to the area of thrombosis and yet in an area where venous interruption will not be followed by disability.

For many years ligation of the inferior vena cava has been done for a variety of reasons. The application to the treatment of phlebitis and its complications [7] was proposed in 1935. Since then the procedure has been reevaluated by several groups and the indications discussed in the light of therapeutic concepts of the time. The indications for inferior caval ligation as proposed by some of these groups [8] are listed in Table 1.

CLINICAL MATERIAL

With present programs of the anticoagulant treatment of venous thrombosis in mind, a review of the place of inferior caval ligation in the treatment of this disease was made. Fifty-nine patients with major venous thrombosis requiring hospitalization, with or without pulmonary emboli, were studied. The anticoagulant regimens were instituted and supervised by many persons and generally followed accepted

TABLE 2.—*Summary on Fifty-Nine Patients with Major Venous Thrombosis Requiring Hospitalization*

Condition	Patients, No.	Patients with Pulmonary Emboli	Caval Ligation		Deaths
			Advised	Done	
Postoperative thrombophlebitis or phlebothrombosis	12	3	..	2	0
Pelvic thrombophlebitis	2	1	1	..	1
Heart disease	18	11	..	..	5
Postphlebitic (chronic)	4	3	1	2	0
Terminal illness	6	5	..	1	4
Post traumatic	6	2	..	..	0
Idiopathic	11	0	..	..	0
Total	59	25	2	5	10

patterns. If venous interruption was considered or done, the patients came under my supervision. These patients and their pertinent data are listed in Table 2 to serve as a background of the experience of one surgeon in the problem of caval ligation. Several of the patients for whom ligation of the inferior vena cava was advised or done are reported on in detail. The findings on these and other patients are summarized in Table 3.

7. Krotoski, J.: Zur Venenunterbindung bzw.-extirpation bei der puerperalen Allgemeininfektion vom chirurgischen Standpunkt, Chirurg **9**:425-439 (June 1) 1937.

8. (*a*) Northway, R. O., and Buxton, R. W.: Ligation of the Inferior Vena Cava, Surgery **18**:85-94 (July) 1945. (*b*) Kirk, G. D.: Ligation of the Inferior Vena Cava for Septic Thrombophlebitis, Am. J. Surg. **73**:606-612 (May) 1947. (*c*) Carpenter, W. S., and Dibble, H. F.: Ligation of the Inferior Vena Cava for Acute Femoro-iliac Thrombophlebitis: Case Report, Harper Hosp. Bull. **6**:85-88 (May-June) 1948. (*d*) Newman, H. F.: Ligation of the Inferior Vena Cava and Ovarian Veins for Infected Abortion, Am. J. Surg. **75**:746-748 (May) 1948. (*e*) Collins, C. G.; MacCallum, E. A.; Nelson, E. W.; Weinstein, B. B., and Collins, J. H.: Suppurative Pelvic Thrombophlebitis: I. Incidence, Pathology and Etiology; A Study of 70 Patients Treated by Ligation of Inferior Vena Cava and Ovarian Vessels, Surgery **30**:298-310 (Aug.) 1951. (*f*) O'Neil, E. E.: Ligation of the Inferior Vena Cava in the Prevention and Treatment of Pulmonary Embolism, New England J. Med. **232**:641-646 (May 31) 1945. (*g*) Oaks, W. W., and Hawthorne, H. R.: Pseudoembolic Phlebitis with Ligation of the Inferior Vena Cava: A Case Report, Am. Surg. **127**:1247-1251 (June) 1948.

TABLE 3.—*Summary of Cases in Which Inferior Vena Caval Ligation Was Performed or Advised*

Case	Age, Yr.	Original Disease	Treatment	Indication for Inferior Caval Ligation	Pulmonary Emboli, No.	Immediate Sequelae	Swelling of the Legs	Comment
1	56	Iliofemoral thrombophlebitis, rt. leg	Heparin	Unilateral iliofemoral thrombophlebitis with pulmonary emboli	3	None	None after 1 yr.	At work on farm in 6 wk.
2	31	Stab wound of abdomen	Heparin	Pulmonary emboli without obvious origin	3	Transient vasospasm of legs	None after 1 yr.	None
3	28	Glioma of brain; lt. iliofemoral thrombophlebitis	Heparin; Dicumarol	Pulmonary emboli, hematuria while on anticoagulants	1	None	None	Died of glioma 2 mo. after ligation
4	29	Umbilical hernia	Heparin	Pulmonary emboli not responding to heparin; no definite origin	3	Swelling of the legs	3-4 cm. circum. increase, with ulceration lt. leg	Wears an aeropulse legging after 18 mo.
5	32	Rt. iliofemoral thrombophlebitis, chronic recurrent	Heparin	Pulmonary emboli	2	None	Swelling of rt. leg (as before)	More ready swelling of involved leg
6	38	Lt. iliofemoral thrombophlebitis	Heparin (regular)	Pulmonary embolus before and while on regular heparin	2	Caval ligation refused; superficial femoral done (bilateral)	Moderate swelling of lt. leg	Femoral vein on left had organized thrombus to groin
7	47	Ischiorectal abscess with extension into space of retzius and pelvis; pelvic thrombophlebitis; bilateral phlebothrombosis	Extensive drainage; anticoagulants contraindicated by large granulating wounds	Septic infarct of lt. middle lobe of lung (embolic); brain abscess	1	Ligation not done because of severe skin contamination	Swelling of both legs	Caval ligation strongly indicated but incision and drainage of lung abscess done first; patient died of massive pulmonary embolus as caval ligation was being arranged

REPORT OF CASES

CASE 1.—A. W., a 56-year-old farmer, was admitted to the hospital on Feb. 14, 1952. Four days prior to admission pain developed in the right leg just above the knee. The pain became severer, radiating into the right groin, and was accompanied by discoloration of the entire right leg. He was unable to walk because of the pain. There were no chills. There had been no chest pain or hemoptysis.

He had been hospitalized five months previously for "acute lumbosacral strain" characterized by low back pain. In 1937 he had had a "clot on the lung" as a complication of an appendectomy.

On admission the temperature was 99.4 F., pulse rate 88, and respiration 20. The patient was muscular; he was not too ill. There was a right transverse scar in the lower abdomen. There was tenderness in the right inguinal region but no abdominal tenderness. The right leg was 4 to 5 cm. larger in circumference than the left leg, in both the calf and the thigh. The right leg was dusky and indurated to the groin. Peripheral arterial pulsations were good in both legs.

Laboratory findings on admission showed a normal urine and a negative reaction to the Kahn test. The white blood cell count was 11,600, with 78% neutrophiles, hemoglobin content 14.4 gm. per 100 cc.; sedimentation rate 23 mm. per hour, and coagulation time 9 minutes. A roentgenogram of the chest was unremarkable.

The patient was heparinized with a combination of regular heparin and Depo-Heparin. The coagulation time for the first 10 days was over one-half hour, with the exception of three periods in which the response to the drugs was unpredictably poor. Four hours after an injection of 300 mg. of Depo-Heparin and 50 mg. of regular heparin on Feb. 24, 1952, the patient experienced sudden and progressively severe left chest pain. The temperature rose to 100.4 F. and the pulse rate to 100. He was very apprehensive. A portable chest film was not helpful. Later that day a pleuritic rub was felt on the left. It was determined to continue heparinization but to urge intervention strongly should any further signs develop. The patient was opposed to surgery.

Seven hours later the patient experienced pain in the right chest and shoulder, with dyspnea and cyanosis. It was felt that this represented a second embolus. The patient was very ill and frightened. He agreed to inferior vena caval ligation. Prior to surgery 50 mg. of protamine sulfate was given intravenously.

With the patient under general anesthesia the inferior vena cava was exposed through a right transverse muscle-splitting incision in the retroperitoneal plane. The vein was bound down by dense fibrous adhesions and scar. It was most difficult to isolate, and in doing so it was torn. After much difficulty the cava was identified at the bifurcation and a ligature placed about both common iliac veins at this point. The cava itself was encircled some 2.5 cm. above the bifurcation and ligated there. In this instance the anesthesia record showed remarkably little variation in view of the difficulties encountered. The right sympathetic chain was cut, but no ganglia were removed.

Immediately after the procedure the legs were warm but mottled. There was no swelling until the patient got up on the fifth postoperative day. Generally, the postoperative course was benign, with only transient febrile periods and some adynamic ileus.

Twenty-four days after the ligation, the patient developed pain in the left leg, which was made worse by walking. This subsided slowly but only after bed rest. The patient went home 33 days after the ligation, wearing compression bandages on both legs (Fig. 1).

He returned to work on his farm six weeks after the procedure but refused to wear his Ace bandages. There was some swelling and aching of the legs in the evenings. Eleven months after the ligation he was working full time with only minimal swelling of the right leg after a hard day. No discernible size difference was noted.

Comment.—This man had had previous venous thrombosis, and the present episode was not controlled by heparinization. The caval ligation was a lifesaving procedure attended by difficulties from a previous inflammatory process of the veins. Despite this the patient has done well with minimal disability.

CASE 2.—G. S. E., a 31-year-old logger, sustained a stab wound of the left upper abdomen 19 days prior to admission. Two wounds in the colon were sutured and a double-barrelled colostomy established in the transverse colon. This was done at another hospital. The patient did quite well after this procedure and went home for his convalescence on the 14th postoperative day. On the 18th day, he experienced pain in the right lower chest and fever and sweating.

The past history was unremarkable.

On examination the temperature was 99 F., pulse rate 108, respiration 35, and blood pressure 134/70. The patient was a husky white man in some pain on respiration. Motion was restricted in the right chest, with diminished transmission of breath sounds in the lower chest.

A well-functioning left transverse colostomy was present. A lower abdominal laparotomy

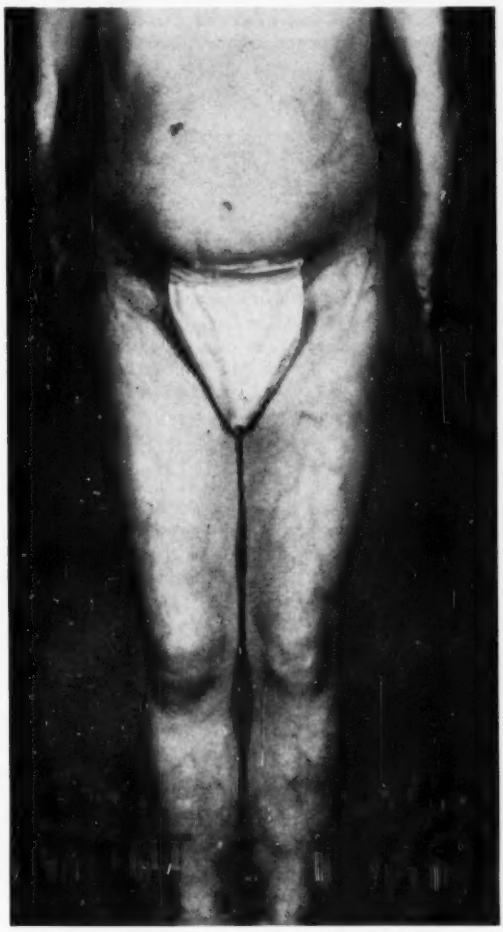

Fig. 1 (Case 1).—Infrared photograph of trunk and legs, taken two months after inferior vena caval ligation. There is little swelling, although the pattern of the superficial veins is somewhat more distinct.

scar and a stab wound scar in the left lower quadrant were fresh and healing well. The extremities were quite unremarkable, without swelling or tenderness.

Laboratory findings were as follows: hemoglobin content, 14.4 gm. per 100 cc. and white blood cell count 7,300, with 75% neutrophiles. The coagulation time was 4 minutes 40 seconds. The urine had a specific gravity of 1.014, with 4 to 6 white blood cells and 2 to 3 red blood cells per high power field.

A roentgenogram of the chest showed blunting of the left costophrenic sinus, with small peribronchial infiltrates in both lung bases.

For two days the patient was comfortable but had an evening elevation of temperature to 99 F. Early on the third day there was sharp right chest pain; a friction rub was felt. The temperature rose to 100.2 F. The patient was heparinized with 200 mg. of Depo-Heparin and 50 mg. of regular heparin.

At 6:30 p.m. (the coagulation time was 27 minutes) the patient had a sudden, severe pain in the left chest. An electrocardiogram showed a normal tracing. A portable chest film showed infiltrates in both bases. While these studies were in progress, another severe pain occurred in the left chest, with coincident pallor, diaphoresis, thready pulse, tachycardia, and loss of recordable blood pressure.

Examination after this last insult showed a faint rub in the left lung base. No signs were present suggestive of venous thrombosis of either extremity. It was felt that there was thrombosis of the deep pelvic veins secondary to an indolent peritonitis. Inferior vena caval ligation seemed essential to save the life of the patient.

After 50 mg. of protamine sulfate was administered intravenously, the patient was taken to the operating room, where, with use of general anesthesia, the inferior vena cava was explored through a right flank muscle-splitting incision. The cava had some adherent scarring that required double ligation immediately above the bifurcation.

Immediately after the procedure the right foot became cadaveric and cold up to the midcalf. This condition lasted for 20 minutes, and subsequently the right foot remained warmer and less moist than the left foot. Both legs showed venous engorgement but no distention.

During the first two days after the ligation, the temperature rose to 101 F., but gradually subsided to normal in a week. The patient was comfortable and free of anxiety. He had some pain in the right groin which radiated around the iliac crest and was severer on activity. He was kept in bed with the legs elevated for five days, then allowed up with Ace bandages around the legs.

Three weeks after the caval ligation the transverse colostomy was closed. Recovery from this was satisfactory; however, there was some pain in the left thigh. The use of Priscoline, heparinization, and paravertebral blocks was ineffective in controlling this discomfort. It subsided spontaneously, and the patient went home 30 days after the colostomy closure, feeling quite well. The left leg was 1 cm. smaller in circumference than the right throughout its length.

Four months later an incisional hernia was noted in the colostomy wound. This was repaired. The patient had pains in the left chest and arm and some dizzy spells. These symptoms kept him from working. The legs were asymptomatic, although the right leg continued to be about 2 in. (5 cm.) larger in circumference (Fig. 2).

One year after the caval ligation no detectable difference was noted in the leg size. The patient was not working because of increasingly frequent periods of dizziness and left chest pain. His weight had increased from 87 to 104 kg. Psychiatric help had been advised but was declined.

Comment.—This man had no obvious site of thrombosis at the time of his pulmonary emboli; however, during his convalescence the swelling of the right leg would suggest that there had been an iliofemoral thrombosis. Caval ligation was a life-saving procedure, indicated by the total lack of response to anticoagulants and by the uncertainty as to the site of the thrombosis. There was no troublesome swelling of the legs one year after ligation. However, because of complicating factors the patient could not be properly rehabilitated.

CASE 3.—R. S., a 28-year-old house painter, had undergone two previous craniotomies for a "mixed glioma" of the right temporal lobe. The last procedure was a palliative right subtemporal decompression done at another hospital in February, 1952. He entered the Veterans Administration Hospital in April, 1952, because of sphincteric disturbances, left hemiplegia, and mental confusion.

On examination vital signs were normal. The patient was an obese, quiet, disoriented young man with left spastic hemiplegia and left hypesthesia. There was a soft pulsating right subtemporal decompression which protruded about 2 cm. The lungs were clear. There was no swelling of the legs.

Laboratory determinations showed a normal blood picture with 17 gm. of hemoglobin per 100 cc. and a white blood cell count of 5,200. The urine contained 50 to 100 red blood cells and 10 to 20 leucocytes per high power field. Culture yielded Klebsiella pneumoniae sensitive to several antibiotics. The spinal fluid pressure was between 240 and 340 mm. of water, depending on the state of the patient. The fluid was normal in constituents. The blood urea nitrogen level remained at 14 mg. per 100 cc.

Skull films confirmed the right parietal defect, and a portable chest film was inconclusive.

Fig. 2 (Case 2).—Photograph taken eight months after caval ligation. Patient would not wear compressive bandages. (Panchromatic XX film.)

Five days after admission the temperature suddenly rose to 101 F. Signs of a "pneumonitis" were detected in the left lung base. The following day tenderness was elicited in the left groin over the femoral vein. There was a 2 cm. increase in the circumference of the left calf. Depo-Heparin was given for three days, the coagulation time being kept at 25 minutes. Bishydroxycoumarin was simultaneously given (150 mg. per day) and the heparin discontinued. On the third day of bishydroxycoumarin administration, gross hematuria was noted. All anticoagulants were discontinued.

Simultaneously the temperature rose to 101 F. Tenderness and swelling in the left leg and groin increased. After serious consideration it was decided that venous interruption was in order, despite the neurological picture. It was hoped that some help could be given the patient for the brain tumor, if he lived.

On the following day the inferior vena cava was ligated retroperitoneally through a right flank incision. There was a transient bout of hypertension postoperatively.

The course was essentially unchanged after the first week postoperatively. The temperature returned to about 100 F., with occasional spikes to 101 F. There was no detectable increase in leg size, temperature, or color.

One month after the caval ligation a reexploration of the intracranial tumor was proposed to the family. This was declined. The patient lapsed gradually into coma and died quietly two months after the ligation. The terminal event was hematemesis and convulsions. No autopsy was permitted.

Comment.—The caval ligation was done in this man as a lifesaving procedure in the hope that something further could be done for his brain tumor. Anticoagulants had been used reluctantly because of the danger of an intracranial hemorrhage. The hematuria offered a ready excuse to discontinue this regimen. The level of ligation had to be above the iliofemoral region. Apparently no harm came from the caval ligation, and no further evidence of emboli appeared.

CASE 4.—E. K., a 29-year-old engineer, entered the hospital 20 hours after pain developed in the abdomen. The pain settled in the right lower quadrant. He was hungry but felt quite ill.

The temperature was 37.50 C. and the pulse rate 88. He was a chubby young man, not in severe pain. The lungs were clear. The abdomen had definite right lower quadrant tenderness, most marked near the umbilicus. The legs were nontender.

The leucocyte count was 7,600 and the serum amylase level less than 200 units. Urinalysis was unremarkable.

Abdominal exploration revealed a gangrenous fat tab in a minute umbilical hernia. The fat tab and appendix were removed.

The temperature rose to 38.7 C. on the second and third postoperative days. Rales were heard in both lung bases at that time; however, they disappeared, and the patient went home five days after the procedure.

He returned to the hospital a week later, sudden severe pain in the right lower chest having developed. The temperature was 38.1 C. Rales were heard in the right lung base. A chest film and an electrocardiogram were not helpful. The leucocyte count was 10,450.

The course was one of rising temperatures and increasing right chest pain. A pleuritic rub was heard in the right lung base. The left calf was found to be tender. Heparinization was started on the date of this finding, a combination of Depo-Heparin and regular heparin being used. The coagulation time remained between 20 and 40 minutes. The chest film showed a pneumonic infiltrate on the left, the right being clear.

Four days after heparinization the patient became confused and more ill, with rising temperature. The chest film showed clearing of the previous infiltrate. The legs were now neither tender nor swollen. Suddenly on the sixth day of heparin therapy the patient became dyspneic and cyanotic. No localizing signs were found. It was agreed by all that inferior vena caval ligation was in order.

With the patient under spinal anesthesia, the cava was ligated retroperitoneally through a right flank incision. No thrombosis was noted in the cava or in the right common iliac.

The following day the temperature began to drop. The sensorium cleared, and a portable chest film showed some clearing. There was swelling of the thighs, bilaterally. The course was one of continuous gradual improvement from then on. There was some pain in the right groin and over the iliac crest, which was relieved by paravertebral sympathetic block. The legs were tired, but the swelling was not troublesome as long as Ace bandages were worn.

Six weeks after the caval ligation, on one examination, there was no swelling. The patient could walk only two to three blocks without tiring, however. Three months after ligation he could walk 2 to 3 mi. (3 to 5 km.) and was working at a sedentary job. Small varices were noted over the abdomen. The patient complained of diminished libido.

Nine months after ligation, there was a 3 to 4 cm. increasing circumference of both legs over their preoperative state, and the patient needed a pneumatic compression boot for the right calf. After this was fitted, he ceased to return to the clinic. He was back at his original job.

Comment.—The first pulmonary embolus was undiagnosed for several days; however, the second one occurred while the patient was being given adequate doses

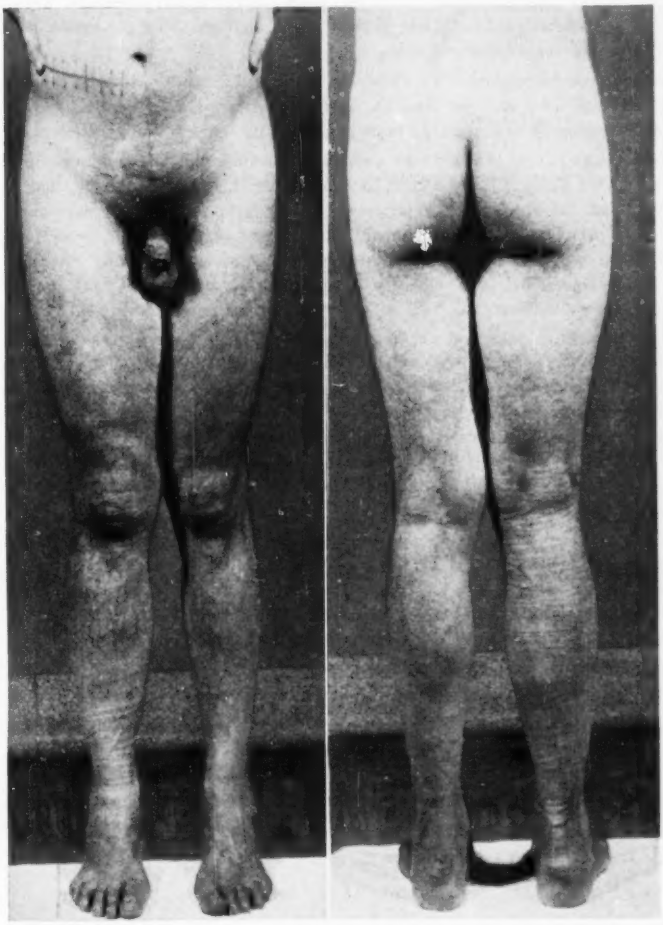

Fig. 3 (Case 5).—Photograph taken five weeks after inferior vena caval ligation. Patient had left hospital against advice, returning with a poorly applied compressive bandage which had just been removed at the time of the photograph. There was no swelling of the left leg, and the right leg was no larger than it had been preoperatively.

of heparin. The origin of these emboli was almost certainly from the veins of the legs or the pelvis, but no localization could be made. Caval ligation was elected because of this fact.

CASE 5.—J. C., a 32-year-old shipping clerk 10 years prior to admission had had his first bout of thrombophlebitis of the right leg, without any apparent cause. The right leg remained

about 1½ in. (4 cm.) larger in circumference than the left, and he had recurrent episodes of pain, aching, and swelling, and on two occasions prolonged hospitalization was required. Three weeks prior to his present admission, the dull aching pain and swelling recurred, being most marked in the thigh and in the groin.

On examination the patient was a moderately obese young man. The temperature was 98.6 F., pulse rate 80, and blood pressure 130/82. The lungs were clear. The only significant findings were confined to the right leg, which was 2 in. (5 cm.) larger in circumference in the thigh and 1 in. (2.5 cm.) in the calf than the left. There was tenderness along the medial aspect of the right thigh, over the saphenofemoral vein.

An admission roentgenogram of the chest was normal. The white blood cell count was 13,100, hemoglobin content 14.6 gm. per 100 cc., and sedimentation rate 24 mm. per hour. The coagulation time (Lee-White) was 17 minutes. Urinalysis showed nothing abnormal.

The patient was put to bed with the extremity elevated, and dry heat was applied to the right thigh and the groin. On the second day the temperature rose to 101 F., and on the evening of the third day the patient experienced severe right lower chest pain aggravated by respiration. Heparinization was instituted with regular heparin and Depo-Heparin. The coagulation time, after establishment of dosage, was kept over 30 minutes. Films of the chest four days after the original pain showed a pleural effusion in the right lung base posteriorly. There was occasional hemoptysis.

The chest pain, thigh pain, and swelling subsided. Heparin administration was discontinued after 13 days; the patient had been symptom-free for 3 days and was ambulating. Suddenly, one week after this event, there was another severe right chest pain, temperature elevation to 101 F., prostration, and extreme apprehension. At first the patient refused all further treatment; then he elected caval ligation, which had been advised shortly after this infarct occurred. This procedure was done, with the use of spinal anesthesia, through a right retroperitoneal approach. The fourth lumbar sympathetic ganglion was removed on the right.

The postoperative course was quite benign. The temperature fell to normal in two days. The chest pain subsided in a most miraculous manner. The whole mental outlook of the patient changed from a sullen, frightened, paranoid one to one of cheerful optimism. He was out of bed with his legs bandaged on the fifth day postligation, with activity increasing rapidly. There was no increase in swelling of the right leg until he began to walk; then, depending on the activity, there was swelling of both legs, which was most marked on the right.

One month after the ligation the patient was readmitted because of disabling swelling of the right leg. This responded to 24 hours of bed rest. An aeropulse legging was prescribed. The swelling was controlled partially by (Fig. 3) this. The left leg had no swelling at all.

COMMENT

From this material it is apparent that inferior vena caval ligation was reserved for those patients who had had one or more pulmonary emboli (Fig. 4). The actual indications from this series would be as follows:

1. Proved pulmonary embolus associated with
   (*a*) Unilateral iliofemoral phlebitis (Cases 1, 5, and 6)
   (*b*) Bilateral common femoral phlebitis (thrombophlebitis or phlebothrombosis)
2. Proved pulmonary embolus without obvious source of the emboli (Cases 2 and 4)
3. Ascending venous thrombosis with a contraindication for anticoagulant therapy (Cases 3 and 7)
4. Pelvic thrombophlebitis with septic pulmonary emboli (Case 7)

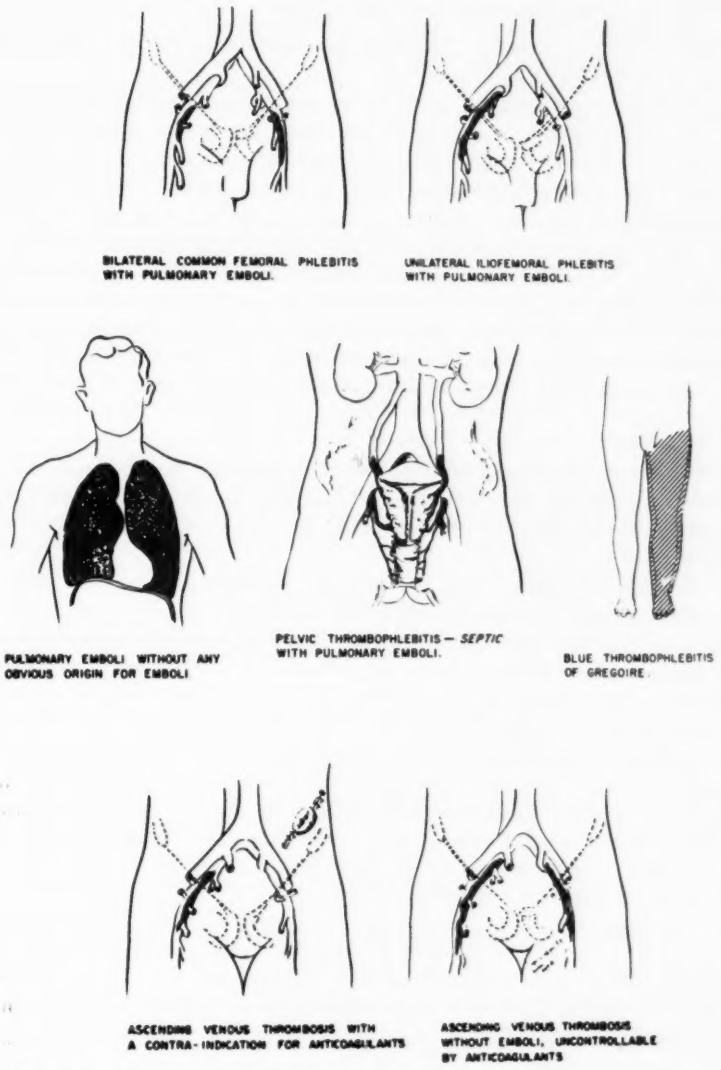
BILATERAL COMMON FEMORAL PHLEBITIS WITH PULMONARY EMBOLI.
UNILATERAL ILIOFEMORAL PHLEBITIS WITH PULMONARY EMBOLI.
PULMONARY EMBOLI WITHOUT ANY OBVIOUS ORIGIN FOR EMBOLI
PELVIC THROMBOPHLEBITIS — SEPTIC WITH PULMONARY EMBOLI.
BLUE THROMBOPHLEBITIS OF GREGOIRE.
ASCENDING VENOUS THROMBOSIS WITH A CONTRA-INDICATION FOR ANTICOAGULANTS
ASCENDING VENOUS THROMBOSIS WITHOUT EMBOLI, UNCONTROLLABLE BY ANTICOAGULANTS

Fig. 4.—Indications for ligation of the inferior vena cava in venous thrombosis.

Two additional indications seem to be clearly demonstrated by the experience of others and should be included:

5. Pelvic thrombophlebitis with pulmonary emboli
   (*a*) In infected abortion with parametritis
   (*b*) Pelvic peritonitis [9] (ovarian vein ligation should be included in the procedure as well)
6. Blue thrombophlebitis of Gregoire [8g] (phlegmasia caerulia dolens). (A corollary of this might be the ascending venous thrombosis of both legs—to the iliofemoral level—without emboli, but uncontrollable by anticoagulants. This circumstance would probably lead to a blue thrombophlebitis very shortly.)

The wider use of caval ligation has been prevented by the fear of producing serious disability or of a high operative mortality. These fears are partially justified; however, from the experiences outlined above, not entirely so. The following, beneficial results of inferior caval ligation in the patient with venous thrombosis are almost entirely immediate: (1) immediate cessation of pulmonary emboli, (2) immediate relief of pain in the involved extremity, (3) immediate relief of the feeling of impending disaster which is often marked in these patients, (4) early rehabilitation with greatly shortened hospitalization, and (5) an operative mortality lower than the mortality of subsequent emboli.

The detrimental effects of inferior caval ligation in the circumstances under discussion are largely late. They are serious and should never be minimized to the patient, but at the same time much can be done to successfully prevent their occurrence.

A. Operative mortality could be significant, although in the present small series there were no deaths from the procedure per se, and few have been reported. These patients are in precarious condition if they have had a massive pulmonary infarct. This in itself makes the procedure dangerous. It is quite striking, however, that immediately after the ligation of the vessel the pulse rate will drop, the blood pressure stabilize, and the condition improve under the eye of the anesthesiologist.

B. Immediate arteriospasm at the time of ligation has not been a serious complication to date, but in Case 2 it was the cause for some concern for a few minutes. It might possibly lead to irreversible damage in an older person. Spinal anesthesia is a good preventative, as well as the excision of a single lumbar ganglion on the side involved. This is easily done at the time of the ligation and may help in the relief of the postoperative inguinal pain.

C. Postoperative aching in the groin and over the iliac crest can be troublesome but is transient. It may be the result of collateral opening through the iliac circumflex and the superficial epigastric systems. Sympathectomy at the time of the ligation or sympathetic block has been effective in controlling these symptoms.

D. Swelling of the legs has not been as serious as anticipated and generally follows the pattern observed by others. There were no women in this group, but

9. Collins, C. G.; Nelson, E. W.; Collins, J. H.; Weinstein, B. B., and MacCallum, E. A.: Suppurative Thrombophlebitis: II. Symptomatology and Diagnosis; A Study of 70 Patients Treated by Ligation of the Inferior Vena Cava and Ovarian Veins, Surgery **30**:311-318 (Aug.) 1951. Colline, C. G., and Ayers, W. B.: Suppurative Pelvic Thrombophlebitis: III. Surgical Technique; A Study of 70 Patients Treated by Ligation of the Inferior Vena Cava and Ovarian Veins, Surgery **30**:319-328 (Aug.) 1951. Collins and others. [8e] Krotoski. [7] Newman. [8d]

the experience of other authors [10] indicates that the swelling is minimal, if it occurs at all, in females. In men, in one instance of the five, swelling achieved serious proportions. In this patient it was of the degree seen in the usual postphlebitic leg. It is the impression from this group of patients that the swelling of the extremities, when it occurs, is no greater than that which would have occurred in the postphlebitic limb without ligation. The superimposed surgical interruption may have been blamed unjustly. A larger series of cases with careful satistical analysis would be required to prove this thesis. Certainly this group shows the truth of the observation of Northway and Buxton [5a] that the final state of the legs cannot be determined in less than a year in some patients.

Much can be done to minimize or prevent the swelling of the extremities. In the immediate postoperative period the legs should be elevated at all times. When the patient is allowed up, he should have compressive bandages properly applied to his legs up to the thighs. He should wear these at all times when he is up, for at least the first three months. If he has pain or heaviness of the legs, he should elevate them immediately and gauge his activity so that these symptoms do not occur. The major premise of the rehabilitation procedure is that it is easier to prevent swelling of the legs than it is to get rid of it once it has occurred.

SUMMARY AND CONCLUSIONS

The treatment of uncomplicated venous thrombosis is largely by anticoagulants at present. The pulmonary embolus which arises prior to or during anticoagulant therapy is a serious mishap. The prevention of this embolus or of recurrent emboli has prompted a review of the role of inferior vena caval ligation in this circumstance. Six indications for caval ligation have been proposed and illustrative cases presented. These indications include the following:

1. Proved pulmonary embolus associated with
   (*a*) Unilateral iliofemoral phlebitis
   (*b*) Bilateral common femoral phlebitis
2. Proved pulmonary embolus without obvious source of emboli
3. Ascending venous thrombosis with a contraindication for anticoagulant therapy
4. Pelvic thrombophlebitis with septic pulmonary emboli, as in
   (*a*) Pelvic peritonitis
   (*b*) Infected abortion with parametritis
5. Ascending venous thrombosis, without pulmonary emboli, but uncontrollable by anticoagulant therapy
6. Blue phlebitis of Gregoire (phlegmasia caerulia dolens)

Ligation of the inferior vena cava immediately stops the pulmonary insults and permits early rehabilitation of the patient. It is a serious procedure when done on patients with recent pulmonary infarction; however, the mortality, as reported by many observers, is less than that of repeated infarction.

The sequelae of inferior vena cava ligation are serious but partially preventable. Swelling of the extremities is confined to the extremities involved by the original phlebitis and is little greater than without caval ligation. The use of elevation and compression bandages helps to diminish this disability.

10. Burch, G. E., and Winsor, T.: Physiological Studies on 5 Patients Following Ligation of the Inferior Vena Cava, Proc. Soc. Exper. Biol. & Med. **53**:135-138 (June) 1943. Duff, Linman, and Birch. [5a]

OVARIAN INFLUENCE UPON SURVIVAL IN BREAST CANCER

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AND
GLORIA GOLDMAN
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FOR YEARS oophorectomy has been advocated in premenopausal cases of mammary cancer as a method of arresting its growth and of increasing the survival time in a significant percentage of cases.

In this study an attempt has been made to determine whether a pathologic alteration of ovarian stroma commonly found associated with breast cancer has retarded or accelerated the malignant disease process. For this purpose the total disease durations in collected cases of untreated and mastectomized patients were compared with breast cancer cases in which the patients were also surgically castrated.

Previous investigation of 100 autopsied cases of breast cancer indicated that, regardless of the age of the patient at cancer onset, in a large majority (83%) of cases the ovaries were abnormal, being characterized by a hyperplasia of the cortical stroma, reflecting active secretion of some steroid hormone.[1] Circumstantial evidence pointed to anterior pituitary hyperfunction as the cause of the ovarian cortical stroma hyperplasia. More recently, findings which can be interpreted as a direct histologic proof of pituitary hyperfunction in human autopsy material from breast cancer cases have been provided by Burt and Castleman.[2]

McManus and Sommers [3] investigated the therapeutic effects of oophorectomy in breast cancer, comparing the 18 available surgical cases in which the ovaries displayed stroma hyperplasia with the 8 instances in which the ovaries were atrophic. The total disease duration found in this previous study in surgically castrated women with ovarian stroma hyperplasia averaged 41 months, median 39 months. This was almost twice the length of life in women with atrophic ovaries, average 23 months, median 22.5 months. The average postcastration survival time in the

This investigation was supported by a research grant from the National Cancer Institute, of the National Institute of Health, Public Health Service—C 1754 (R).

From the Departments of Pathology, Pondville Hospital (Massachusetts Department of Public Health), Walpole, Mass., and Harvard Medical School, Boston; the Cancer Research Institute, New England Deaconess Hospital, and Harvard Cancer Commission, Boston.

1. Sommers, S. C., and Teloh, H. A.: Ovarian Stromal Hyperplasia in Breast Cancer, A. M. A. Arch. Path. **53**:160, 1952.

2. Burt, A. S., and Castleman, B.: Some Histological Effects of Estrogens and Castration on the Anterior Pituitary in Women with Carcinoma of the Breast, Cancer **6**:236, 1953.

3. McManus, R. G., and Sommers, S. C.: Breast-Cancer Prognosis and Ovarian Cortical Stromal Hyperplasia, New England J. M. **246**:890, 1952.

group with ovarian hyperplasia was 56% of the total average duration of disease, as compared with 28% for the women with atrophic ovaries. Owing, perhaps, to the small size of the groups, the findings had no statistical significance.

PRESENT STUDY

It appeared desirable to determine whether the survival periods of women with intact ovaries, who had breast cancer, whether mastectomized or unoperated on, were influenced by the presence or absence of ovarian cortical stroma hyperplasia, regardless of the age of the patient at cancer onset. For this analysis, records of autopsied cases of breast cancer in which ovaries were available for microscopic examination were collected from the files of the Pondville Hospital (Massachusetts Department of Public Health) and from the New England Deaconess Hospital.

A total of 125 suitable cases were found, including the 100 cases with ovaries previously studied pathologically.[1] Other cases in which ovarian microscopic sections were inadequate or were heavily infiltrated by metastatic carcinoma were excluded. No cases in which the patients had been surgically castrated were included in the autopsy series. Of the 125 cases, there were 102 (82%) in which the patients had ovarian cortical stroma hyperplasia and 23 (18%) in which the ovaries were atrophic. The presence of nodular cellular cortical masses of whorled plump spindle cells with or without extension into the ovarian medulla was considered diagnostic of stroma hyperplasia.

As in the previous study of postcastration survival,[3] the total disease duration was determined, by review of the histories, from the time when the patient first noted a mass in the breast until death.

RESULTS

No significant differences were found in the total disease durations of breast cancer, when comparisons were made, contrasting the patients with ovarian stroma hyperplasia with those having atrophic ovaries, in the following groups: (1) all autopsied cases, (2) patients not mastectomized, (3) patients with mastectomy. Analysis of groups of cases in which the patients were either over or under 45 years of age also showed similar distributions of survival periods.

For the total group of 102 autopsied cases in which there was ovarian cortical stroma hyperplasia, the average total disease duration was 34 months, the median 26 months, and the range between 2 months and 12 years. The 23 women with atrophic ovaries had an average total disease duration of 31 months, median 17 months, and the limits were 1 month to 12 years 2 months (Table 1).

Included were 45 women on whom no mastectomy was performed, and the disease duration was known in 38 of these. For the 30 women with ovarian stroma hyperplasia, the average survival from onset of breast cancer was 21 months, with a range of 3 months to 7 years. For the 8 women with atrophic ovaries the average total duration was 18 months and the range 3 months to 5 years. The respective median survival times were 14 and 12.5 months.

Among the 72 mastectomized women with ovarian stroma hyperplasia, the mean total disease duration was 39 months, as compared with 38 months for the 15 women with atrophic ovaries. A comparison of postmastectomy survivals without castration showed little difference, since the average postoperative survival time

of 68 women with ovarian cortical stroma hyperplasia was 29 months, with limits of 2 days to 8 years, as against 27 months for 15 women with atrophic ovaries, durations ranging between 3 days and 8½ years.

However, an unexpected difference in survivals was found by reexamination of the previously reported series of breast cancer cases in which the patients were mastectomized and surgically castrated, as compared with the present autopsy series in which the patients were mastectomized but not castrated (Table 2).

The mean survival of 14 mastectomized patients with ovarian stroma hyper-

TABLE 1.—*Total Disease Duration in 125 Autopsied Breast Cancer Cases*

Months	Ovarian Stroma Hyperplasia	Ovarian Atrophy
0- 12	28	10
13- 24	22	8
25- 36	15	3
37- 48	11	3
49- 60	12	1
61- 72	2	1
73- 84	4	0
85- 96	3	0
97-108	4	1
109-146	1	1
	102	28

TABLE 2.—*Total Durations of Breast Cancer in Months*

	Ovarian Stroma Hyperplasia		Ovarian Atrophy	
	Average	Range	Average	Range
Ovariectomized				
Mastectomy	47	19- 87	29	15- 42
No mastectomy	21	6- 33	12	3- 20
Total	41	6- 87	23	3- 42
Noncastrated				
Mastectomy	39	2-144	38	1-146
No mastectomy	21	3- 84	18	3- 60
Total	34	2-144	31	1-146

plasia was 47 months with oophorectomy, as compared with 39 months, noted above, for those without castration. The total disease durations for mastectomized women with atrophic ovaries averaged 38 months, as already stated, and 29 months for the 5 castrated patients. Owing to the small number of cases available, no statistical significance of this observation could be established.

COMMENT

For this analysis, many factors have necessarily been disregarded in comparing two groups with differing ovarian histology. Inaccuracy of histories as a basis for estimating the duration of breast cancer; the age of patients; cancer site, extent, and operability; the adequacy of surgical removal; axillary lymph node morphology, and the number of metastases, and intercurrent diseases; all have been shown to play roles in determining longevity in mammary cancer.

Once a diagnosis of breast cancer was established, however, and regardless of such etiologic elements as pituitary-ovarian or pituitary-adrenal dysfunctions, or otherwise, the presence and the condition of the ovaries appeared to constitute factors which may be active in determining the further duration of life.

The unanticipated result of an analysis of survival times after various surgical procedures was that the removal of ovaries having ovarian stroma hyperplasia, following mastectomy for breast cancer, was associated with the most prolonged average survival. No particular benefit attended the castration of women who had atrophic ovaries, and in all therapeutic categories this group had shorter disease durations.

To produce maximally prolonged survivals it was thus necessary (1) to remove the primary breast cancer with its regional lymph nodes, and (2) to remove the abnormally active ovarian tissue. This implies that one important factor was the excision of the major source of new metastases. Once this was accomplished, it appears that the metastases already established proved rather dependent upon some secretion from the hyperplastic ovarian stroma. After castration these metastases would seem to have regressed or become dormant for periods of some months.

Since the patients with atrophic ovaries had more rapid courses and were, if anything, adversely affected by castration, some other source of breast cancer growth stimulation seems probable. The adrenal cortex is most likely involved. Perhaps this is the most eligible group for the bilateral adrenalectomy operation introduced by Huggins.

In the past, ovariectomy has not been considered therapeutically in postmenopausal women with breast cancer, on the theory that their ovaries were inactive. Present evidence, however, is that with either endometrial cancer or breast cancer, abnormally hyperplastic ovaries may be present both before and after the menopause. Consideration might therefore more frequently be given to oophorectomy in older women with breast cancer, as a means of prolonging their lives and as an adjunct to medical or surgical therapeutic attempts to alter the endocrine environment.

SUMMARY

The duration of life after onset of disease in 125 autopsied cases of breast cancer was reviewed, contrasting 102 cases (82%) with ovarian cortical stroma hyperplasia with 23 (18%) in which the ovaries were atrophic. The average total disease durations without castration in the two ovarian groups were nearly identical, when all cases of mastectomized and untreated women were separately analyzed. For patients both mastectomized and castrated in another series, the comparable total disease durations differed considerably: 47 months for those with ovarian stroma hyperplasia and 29 months for those with atrophic ovaries. It is suggested, but not proved statistically, that in mastectomized women with ovarian stroma hyperplasia castration was beneficial in prolonging life. Ovariectomy should be considered in patients with breast cancer who have this ovarian condition, both before and after the menopause.

Olive M. Lombard, Biostatistician and Research Associate in Cancer Control, performed the tests for statistical significance.

PATHOLOGIC DIAGNOSES IN AND BASES FOR ONE THOUSAND HYSTERECTOMIES

MARK C. WHEELOCK, M.D.
AND
ANTHONY PIZZO, M.D.
CHICAGO

THIS STUDY was made with two purposes: first, to compile a statistical table of the frequency of certain anatomic changes in the uterus and, second, to learn in how many hysterectomies there is a pathological basis for surgical intervention. Attempts to find an accurate summation of lesions have not been successful. The review was strictly objective by members of the pathology department.

In compiling data, recourse was had to the pathologic reports with no use of records for histories, physical findings, and operative description except for verification of cases of prolapsed uteri.

Total excision of the uterus was done in 930 of these cases; thus only 70 were supracervical in character.

METHOD OF ANALYSIS

The figure 1,000 was selected with the thought that it was large enough to permit of statistical computation and sufficiently small to allow ease of interpretation. Futhermore, with use of 1,000 cases, the study covered a brief span so that no dramatic alteration in concepts on the subject could occur during the intervals. Because the accumulation of data started in June, 1949, a retrogressive period was studied in order to be as objective as possible. To obtain the 1,000 cases, it was necessary to go back to April, 1945, approximately a four-year period, or 250 cases per annum. Because we were thoroughly familiar with most of the specimens analyzed, it was necessary to review only the pathologic report. However, in questionable cases, the slides were read again, and, if needed, additional ones were cut and stained.

The clinical data were analyzed only in that group in which no pathologic diagnosis had been recorded and in the cases of prolapse.

In many instances more than one diagnosis of the material was made. However, only that most important lesion, which was thought to be the primary one, was taken as the cause for the operation.

Passavant Memorial Hospital is a teaching unit of Northwestern University Medical School. All of the attending gynecologists have faculty appointments. Eleven members of the department of gynecology and obstetrics either performed or supervised the hysterectomies.

Present Address: Bloomington Hospital, Bloomington, Ind. (Dr. Pizzo).

From the Department of Pathology, Passavant Memorial Hospital, and Northwestern University, Medical School.

By established agreement, all tissues are studied by both the department of gynecology and obstetrics and the department of pathology. The specimens are first brought to the laboratory of pathology in the hospital, where they are weighed, measured, described, and sectioned for microscopic study. This is done by residents in pathology under the supervision of the pathologist, who is also a faculty member in his respective department at the Medical School. Later the material is studied by the department of gynecology under the direction of any one of a number of gynecologists who have been trained in and are particularly interested in gynecologic pathology. Each department furnishes the other with duplicate reports and, where desired, microscopic sections. By this dual inspection, it is doubtful whether any minute tissue alteration is overlooked.

One Thousand Uteri and Adnexa When Excised

Pathologic Lesions	Frequency Found	Single Diagnosis as Basis for Operative Removal
Leiomyomas (fibromyomas, fibroids, myomas)	607	446
Prolapsed uterus	109	109
Endometriosis	97	89
Adenomyosis	90	77
Pelvic inflammatory disease	162	76
Gravid uterus	36	30
Carcinoma of corpus	36	36
Polyp of endometrium	123	30
Atypical endometrial hyperplasia	61	18
Ovarian neoplasms		19
Nonmalignant	27	2
Malignant	14	14
Cysts	38	3
Polyps of endocervix	61	9
Carcinoma of cervix (squamous cell)	6	6
Sarcoma (leiomyosarcoma)	3	3
Mixed mesodermal tumor	1	1
Choriocarcinoma (chorioepithelioma)	1	1
Ectopic tubal pregnancy	3	1
No pathologic diagnosis	43	40
Chronic cervicitis	700	0

In the present analysis recourse was had to the reports, the specimens, and the slides from both departments. With allowance for slight differences in nomenclature, there was marked concurrence of conclusions, thus simplifying the study.

INTERPRETATION

Interpretation of the Table is aided by considering its arrangement. Commonly accepted pathologic diagnoses are utilized. The number of times each pathological entity was found in the respective instances was recorded and listed in the column "Frequency Found." From this was selected the single main diagnosis, which, in our opinion as pathologists, suggested the need of surgical excision. For instance, either cervical or endometrial polyps might be associated with adenomyosis or leiomyomas of the uterus. However, they were selected as the primary cause for operation only in those instances in which they were quite large, were necrotic and ulcerated, or showed evidence of being the sites of much bleeding.

As would be expected, leiomyomas (including the "fibroid," the fibromyoma, the fibroleiomyoma, the leiomyofibroma, the myoma, and whatever term is used to define the commonest uterine tumor, which is composed mostly of muscle and which often undergoes various forms of cellular and acellular degeneration) constitute a high figure. No attempt was made to base our interpretation on location, size, or number of lesions in the uterus. The preferential listing was based on the selection of some entity other than the leiomyoma as the cause for hysterectomy. This particularly applied to the malignant tumors. Hence, the reasons for the difference in number between the frequency found and the single basis for removal; this despite the established practice of accepting the presence of such leiomyomas as a standard basis for excision.

In the cases of prolapse it was necessary to turn aside from objective study. Had it been possible to study these cases prior to operation, an objective diagnosis could have been made. It is not common practice in hospitals for pathologists to see *in situ* specimens. Even so, in a large number of instances it was possible to determine prolapse by the wide vaginal cuff, the elongated cervix, the thick mucosa, and on section the amount of hypertrophy and cornification of cervical epithelium. All cases of prolapse were interpreted as requiring intervention.

Endometriosis, when diagnosed, was usually widespread. Often implants grew in ovaries, on oviducts, on perimetrium, in peritoneal reflections, on peritoneum, and elsewhere. When extensive, this was treated by hysterectomy as well as by ovariectomy, bilateral. Adenomyosis was nearly as common and also required removal. Usually the lesion was diffuse in the uterine body and, though associated with a leiomyoma or a polyp, was interpreted as the basic cause for radical treatment.

Pelvic inflammatory disease was much commoner in the first two years, after which the influence of antibiotics and of sulfonamides was noted. Of 162 instances of pelvic inflammatory disease we accepted 76 cases in which the condition was sufficiently severe to require more than conservative management.

Of the 36 cases of gravid uteri there were six in which there was no obvious anatomic change. These may have been associated with known toxemias or with other medical problems. Of the remaining 30, the changes were leiomyomas in 24, placenta accreta in 2, retained secundines in 2, rupture in 1, and bicornuate uterus in 1. Some question may arise over placing placenta accreta in this category.

The corpus carcinomas, the sarcomas, the mixed mesodermal tumor, and the choriocarcinoma all justified surgical removal for proper therapy. The six cervical carcinomas were of low grade and were limited in extent. In addition, these lesions were treated by standard radiation.

Of the total number of endometrial and cervical polyps, only approximately one-fifth were considered to be sufficiently large or altered to indicate uterine excision. In somewhat less than a third of the cases of atypical endometrial hyperplasia was radical treatment carried out.

Because of the known tendency for malignant tumors of ovary to spread to the uterus, the uterus was removed in all 14 instances. In 2 of the 27 nonmalignant tumors and in 3 of the 38 cystic ovarian tumors there were also indications for an accompanying hysterectomy. This was done in only one of the three ectopic tubal gestations.

Of all the pathologic diagnoses made, by far the commonest was chronic cervicitis. Some question arises as to the strictness of the histologic criteria. There are also known fashions and clichés in medicine, and certainly chronic cervicitis is one of them. We recorded it 700 times. In order to remain exacting, we eliminated it as a basis for hysterectomy even though there are perfectly obvious instances in which operative removal is required. Some will disagree with this strictness.

In the final analysis there were 43 cases with no pathologic diagnoses considered to be sufficiently altered to justify total excision of the uterus. With clinical study, it may be that there were more than adequate reasons, particularly persistent bleeding with anemia. However, this was an objective study with recourse to the records only in cases of prolapsed uteri. No attempt will be made therefore to explain this small group.

COMMENT

It is doubtful whether anyone will question the column "Frequency Found." Some may not agree on its simplicity or with the method of nomenclature. Others may even ignore the value of or need for this information. Certainly, there have been several occasions on which we were pleased to have such data at hand. At some time we may compare this study with subsequent 1000's of similar cases. Thus we shall determine increase or decrease in incidence, fashions in single diagnosis or in groups of diagnoses, and ability to recognize presence or absence of endometriosis, etc.

The second column in the Table of a single entity being the basis of hysterectomy, would definitely arouse disagreement. Differences will be expressed over the complete elimination of chronic cervicitis as a cause. Some will challenge the inclusion of endometriosis and of cervical polyps. We did in the latter instance and held the number of cases to a minimum. There will be insistence that a case combining a myoma and adenomyosis should possibly have been placed in the former group instead of the latter, or vice versa. No single person or group of persons will make the same interpretation in all cases; however, most will concur regarding the diagnosis in the majority. For this reason, we believe that definite value lies in the study and in the break-up in the two columns.

Finally, we are impressed with one conclusion, that the presence of a pathologic change necessitating a hysterectomy was extremely high. In this consecutive series of 1,000 instances, a specific anatomic diagnosis was made in 957 cases, leaving only 43 to comprise the group with no diagnosis. There may be some indication for not adding the six cases of gravid uteri with no other abnormality. If so, the positive figure would drop to 951.

SUMMARY

An analysis was made to determine (*a*) the number of times specific pathologic entities were found in 1,000 consecutive hysterectomies, and (*b*) the anatomic change necessitating the removal in 1,000 consecutive surgical excisions of uteri.

In over 95% of 1,000 hysterectomies there was a pathologic basis for the procedure.

TRENDS IN ORTHOPEDIC SURGERY

PAUL R. LIPSCOMB, M.D.
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IN HIS presidential address at the annual meeting of the American Academy of Orthopaedic Surgeons, held in Chicago, on Jan. 27, 1953, Dr. Francis M. McKeever,[1] of Los Angeles, stressed the need for basic investigation in orthopedic surgery. He urged that the Committee for the Advancement of Orthopedic Surgery, instituted at the suggestion of the past Academy president, Dr. Guy Caldwell, of New Orleans, be charged with the responsibility for an early attack on the problems of stimulating basic research in orthopedic surgery. Dr. McKeever concurred in the idea that the Academy create a lay affiliate, composed of men representative of many segments of our population, for advice concerning ways in which orthopedic surgery as a specialty may best attain its objectives and serve the public. He envisaged such a group as a powerful stimulus toward furthering basic investigation.

FEMORAL HEAD PROSTHESES

At the same meeting Dr. Claude N. Lambert,[2] of Chicago, chairman of the Committee on Scientific Investigation of the Academy reported the results of a preliminary survey on femoral head prostheses. Questionnaires sent to the total Academy membership of 1,580 were returned by 587 (37%) members. A total of 466 of the 587 reported that they were using femoral head prostheses and 121 were not using them. The members replying had used 5,082 prostheses as of Oct. 1, 1952. The average follow-up time, since this was a preliminary survey, was only 10.3 months. Thirty-seven types of prostheses had been used. The Gibson posterolateral incision was favored almost twice as many times as the Smith-Petersen anterolateral approach. The two commonest indications had been nonunion in 315 instances and aseptic necrosis in 299 instances. The two commonest contraindications listed were patients too young (less than 40 to 65 years of age) and recent infection. The leading complications noted were dislocation, infection, and fracture of the femoral shaft or trochanter.

From the Section of Orthopedic Surgery, Mayo Clinic.

Dr. Paul R. Lipscomb has been appointed Chairman of the Committee of Orthopedists (Dr. Alvin J. Ingram, Memphis; Dr. F. R. Thompson, New York; Dr. John H. Allen, University of Virginia Hospital, Charlottesville, Va.; Dr. M. R. Urist, Los Angeles, and Dr. C. A. Luckey, Stockton, Calif.) to send to the A. M. A. ARCHIVES OF SURGERY a periodical report of the trends and developments in the field of orthopedic surgery. This is the first of such articles.

1. McKeever, F. M.: The Need for Basic Investigation in Orthopaedic Surgery, J. Bone & Joint Surg. **35-A**:285-288, 1953.

2. Committee on Scientific Investigation of the American Academy of Orthopaedic Surgeons: Preliminary Survey on Femoral-Head Prostheses, J. Bone & Joint Surg. **35-A**: 489-494, 1953.

Dr. Lambert and his committee listed the following impressions from the survey: 1. Too many prostheses are being used for too many indications. 2. The trend is toward abandonment of the Judet prosthesis made of acrylic. 3. There is increased use of intramedullary types of prostheses. 4. The Gibson approach is used the most commonly. 5. Indications for the use of such prostheses are becoming more definite. 6. The complications are too great. 7. The survey is to be continued until there is a follow-up time of three to five years. An attempt to evaluate results then can be made.

THE BONE BANK

It is now recognized by most authorities that bone from the bone bank is not as good in most instances as autogenous bone grafts. Nevertheless, preserved bone has its place in certain instances. It often can be used to supplement autogenous bone in extensive spinal fusions, in the obliteration of traumatic, chronic osteomyelitic, cystic, and benign neoplastic defects, and also as bone plates for fixation of certain fresh fractures. Freeze-dried bone stored in vacuum containers at room temperature is being used quite successfully in a number of carefully selected cases by the Medical Corps of the United States Navy. Carefully controlled investigation along this line has been carried out by Lieutenant Commander G. W. Hyatt [3] and his colleagues for several years.

HYDROCORTISONE ACETATE (COMPOUND F ACETATE)

The proper indications for the use of hydrocortisone acetate are now being recognized. This preparation seems to exert its maximal effect when injected locally and can be used in comparatively small doses and without the side-effects of its parent, cortisone. The effect of a single injection usually lasts from 5 to 12 days. It may be helpful in allaying pain and restoring motion in traumatic conditions of the joints, acutely painful shoulders, and post-traumatic bursitis in the vicinity of any joint or protuberance of bone. It seems to be of value also in the treatment of nonarticular rheumatoid arthritis and at times in other rheumatoid joints, particularly the knees. Atlhough it gives temporary relief from pain when injected into some osteoarthritic joints, it is neither practicable nor feasible to inject the substance repeatedly into any joint, week after week for an indefinite time. The chief value of hydrocortisone therefore seems to be in hastening resolution of the inflammatory process, which by its nature is self-limited, in joints and bursae.

FRACTURES

Intramedullary Fixation.—Intramedullary fixation is not the panacea for the fixation of fractures that many seemed to think was the case two or three years ago. It is, however, the procedure of choice for the fixation of many fractures of the shaft of the femur in adults. Occasionally intramedullary fixation may be indicated in fractures of the other long bones, but in most instances fractures in these bones can be treated best by some other method.

Forearm Fractures in Children.—It has been recognized for years that among children growth corrects a remarkable amount of deformity resulting from frac-

3. Kreuz, F. P.; Hyatt, G. W.; Turner, T. C., and Bassett, A. L.: The Preservation and Clinical Use of Freeze-Dried Bone, J. Bone & Joint Surg. **33-A**:863-872; 888. 1951.

tures. Drs. John C. Ivins and Raymond G. Giberson[4] (Rochester, Minn.) recently have analyzed a series of fractures of the distal third of the forearm in children. They have pointed out just how remarkable this correction factor is in these fractures. They concluded in the event that accurate reduction is not obtained or should angulation recur it is better to accept something less than perfect reduction than to perform repeated manipulations or open reduction. If angulation is less than 30 degrees in a greenstick fracture, Drs. Ivins and Giberson feel that reduction is not necessary. They also noted that minor displacement of the radial epiphysis may be left unreduced and that repeated manipulation and open reduction are not indicated, since normal restoration of alignment will take place in the presence of displacement if the epiphyseal cartilage has not been damaged.

Improved Treatment of Fractures.—Every war brings improvement in the treatment of trauma, and World War II and the Korean conflict have not been exceptions from this standpoint. Especially noticeable has been the apparent decrease in the incidence of nonunion of fractures during the last 10 or 12 years. Before 1940 orthopedic surgeons spent much of their time treating ununited fractures which had resulted, in many instances, after simple fractures. Many of these ununited fractures could then be traced to inadequate immobilization. It was not unusual to see short-leg casts used for immobilization in cases of fracture of the shaft of the tibia, long-leg casts for fractures of the shaft of the femur and short-arm casts for fractures of both bones of the forearm. It is now extremely rare to witness examples of such inadequate immobilization.

Most ununited fractures seen by the orthopedic surgeon today are the result of severe compound fractures or distraction. Oftentimes there has been an appreciable loss of bone substance at the time of the injury. Distraction usually can be traced to too vigorous and prolonged skeletal traction or to metal plates and screws which hold apart the fractured ends of the bone concerned. If a metal plate is to be used, and many surgeons have abandoned them completely, the slotted types which allow for absorption at the site of the fracture are preferred. When a plate seems absolutely necessary, some surgeons prefer the primary bone plate or graft. In the case of uncomplicated fresh tibial fractures requiring open reduction and fixation with more than one or two screws, it takes only a few more minutes to secure the fracture with a sliding bone graft, rather than with a conventional type metal plate. The few extra minutes spent in performing a primary bone-grafting operation may save the patient months or even years of disability.

Likewise, the importance of active exercise of every joint that does not need to be immobilized has been learned by practically everyone who takes upon himself the responsibility of treating fractures. Before World War II it was not too uncommon to see stiff rigid hands after Colles' fractures which had been treated by splinting or casting from the tips of the fingers to the elbow. Now we rarely encounter such a complication. Almost all physicians and surgeons and many patients now know that a cast applied for Colles' fracture should allow free motion of the fingers, including the metacarpophalangeal joints.

4. Giberson, R. G., and Ivins, J. C.: Fractures of the Distal Part of the Forearm in Children: Correction of Deformity by Growth, Minnesota Med. **35**:744-749, 1952.

Case Reports

GENERALIZED CALCINOSIS IN A CASE OF PRIMARY LYMPHOSARCOMA OF RETROPERITONEAL LYMPH GLANDS

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IN REVIEWING the literature, I have seen very little mention of malignant tumors considered as one of the etiologic factors in the production of calcinosis. In fact, no specific example seems to have been reported. The purpose of this report is to present the findings in a case of calcinosis in which metastatic lymphosarcoma was present.

REPORT OF CASE

W. D., a 9-year-old white boy, was admitted to the Albany Hospital with a history of having been in good health until one month prior to admission. He then complained of general malaise and pain in the thighs and in the upper part of the right arm. The pains were quite constant and were aggravated by various positions; movements of the right arm were painful in the right shoulder joint. The patient had been confined to bed during three weeks of his illness. An afternoon temperature of 100 to 101 F. was an almost constant factor. Frequent vomiting of a projectile type was present. The patient's family physician had had serum tests taken for the detection of typhoid and paratyphoid groups, as well as for abortive fever; all reactions were negative. Frequent blood cell counts were taken and showed a quite normal red and white blood cell count; the eosinophiles had at one time risen to 5%, but this was not constant, although a lymphocytosis up to 40% in the differential counts was present at all times. No improvement having occurred, the patient was admitted to the hospital.

Physical examination at the time of admission revealed an undernourished child, with evidence of recent weight loss and a flushed appearance to the face. Mucous membranes were pale; the pupils were equal and reacted normally to light and accommodation. The tongue was coated, protruded in the midline, and had a slight tremor. The teeth were good; tonsils were absent, and the pharynx appeared normal. The neck showed no adenopathy, and there was no evidence of thyroid gland enlargement. The thoracic cage was devoid of fat; the intercostal spaces and the supra- and infraclavicular fossae were prominent. The apex beat was in its normal position. Pulmonary and cardiac sounds were apparently normal. The right arm was held tightly to the side, and a slight swelling of the upper arm just below the joint was noted on the lateral aspect. It was quite noticeable that the patient guarded it from movements. In this area, tenderness was noted on deep palpation. The swelling was hard and irregular. There was tenderness in the cervical spine, and there was muscular rigidity in this area when the patient attempted to move his head. There was, however, no evidence of true neck rigidity. The axillary glands were not enlarged. The abdomen showed no evidence of tenderness or spasticity. No masses of any nature were evident. The liver and spleen were apparently normal in size and position. The inguinal glands showed no enlargement. The lower extremities were normal in appearance, but slight tenderness was noted on palpation of the upper third of the right femur. Movements of the hips were normal in all respects. The reflexes were physiologic. Blood pressure was 110/75; temperature 100 F.; pulse 108; respirations 22. Urine showed a trace of albumin and was alkaline; microscopically it was normal. The Bence Jones protein was not found. Blood studies gave the following values: hemoglobin 80%; red blood cells 3,940,000; white blood cells 7,200, with polymorphonuclear neutrophiles 66%, E.O.B.O.L. 26%, monocytes 8%; platelets normal; nonprotein nitrogen

From the Department of Surgery, Albany Medical College, and Albany Hospital.

34.6 gm. per 100 cc.; protein 9.2 gm. per 100 cc.; serum albumin 6.3 gm. per 100 cc.; serum globulin 2.7 gm. per 100 cc.; calcium 14.9 mg. per 100 cc.; phosphates 2.02 mg. per 100 cc.; alkaline phosphatase 3.8 Bodansky units.

Four days after admission and while under gas anesthesia, the upper portion of the humerus was explored. The periosteum was softened and easily cut, and the bone was exposed. This was irregular, spicule-like in character; the bone marrow was seen to be of white, almost homogeneous nature, and a large amount of it was curetted, leaving an extensive medullary cavity. The wound healed primarily, and at the parent's request the boy was allowed to go home and subsequently was requested to report as soon as the microscopic report had been made. A few days later the laboratory report from Dr. Arthur Wright, Pathologist at the Albany Hospital, was incorporated in the hospital chart. The microscopic description of the curettings from the humerus read as follows: "The sections show fragments of bone which are undergoing absorption. The marrow often contains lymphocytes, eosinophiles and giant cells. There is no histological evidence of tumor." The diagnosis was indefinite and was considered as (*a*) osteitis fibrosa cystica and (*b*) Hand-Schüller-Christian disease.

The patient was readmitted to the hospital a few days after his discharge. An almost incessant vomiting had taken place, and the child was becoming weaker and more emaciated. Headache, especially of a right parietal and temporal type, together with pain in the back of the neck, gave the patient such discomfort that he was unable to rest during the day or night unless vigorous medication was employed. There ensued, shortly after hospitalization, severe pain in the two femurs, together with a slight discomfort in the left humerus. At times numbness was present. Appetite was becoming poorer, and it was impossible to persuade the patient to take nourishment. All reflexes had become diminished, but no pathologic reflexes were elicited.

Firm subcutaneous nodules were noted all over the body, varying in size from that of a small pea to that of a large hazelnut; these were most especially found over the abdomen; the nodes were hard, freely movable, regular, and nontender.

Six weeks after his original admission the patient was transferred in an ambulance to his home. Occasional vomiting not preceded by nausea occurred almost daily. Marked tenderness developed about the middle shafts of the femurs and humeri. The pain at no time extended to the tibial area. During this period the calcium deposits, which began to appear while the patient was still in the hospital, grew rapidly. They appeared to be directly under the skin along the shafts of either femur, not adherent to the bone, and freely movable. The patient's appetite was very poor as regards a normal diet, but he was desirous of eating great quantities of fruits, such as watermelon, plums, and cherries. A steady loss of weight ensued. A definite ptosis of the left eyelid developed, and a lateral deviation of the eye was noted. Coincident with this was vomiting of a projectile type. For a few days the patient improved; he began to eat a selected but almost general diet, and the eye deviation disappeared. However, the eyelids became edematous, producing a most grotesque facial expression. About one week later the calcium deposits were noticeably smaller, and they continued to decrease in size. An irritating cough developed, and he was becoming more anemic.

Five weeks later the boy was readmitted to the hospital for blood examination, roentgenograms, and a blood transfusion. He was in the hospital for one day. On his return home and up to the time of his death, symptoms became progressively worse, and itching became most pronounced. Many enlarged lymph glands, axillary and inguinal, developed; they were not painful. A mild delirium occurred from time to time. Ptosis of the right eyelid (instead of the left) developed, and vomiting occurred each afternoon at exactly the same hour. Coughing became more troublesome. The child became extremely emaciated, and he began to complain of a sore tongue. Twelve hours later an area the size of a dime which was hard, red, and indurated appeared. This became purple in color and soon became a gangrenous dirty ulcer.

Approximately seven months from the time of onset of symptoms the patient died.

Roentgenographic Examination.—There were localized destructive changes in the shaft of the right humerus extending 7 cm. distally to the proximal epiphyseal line. There were similar changes throughout the shaft of the right scapula. There were small patches of decalcification in the skull, sacrum, either ilium, the superior and inferior rami of the pubis on the two sides and in the region below the greater trochanter of either femur. There were slight changes in the distal ends of either femur close to the epiphyseal line. There were slight destructive changes in the shafts of the tibiae just distal to the proximal epiphyseal lines and in the shaft of the right fibula under

the proximal epiphysis. Destructive changes were noted in the dorsal and lumbar vertebrae. Decalcification was visible in the 2d and 7th ribs on the left side and in the 3d, 7th, 8th, 9th, and 11th ribs on the right side.

Subsequently (two months later) there appeared a pathologic fracture of the superior ramus of the pubis on the left and of the right femur at the level of the lesser trochanter. Destructive changes in the radii and ulnae and phalanges of both hands and feet were noted. Calcification of the soft parts of the body became visible.

Summary of Autopsy Report.—Autopsy revealed the presence of scattered areas of calcification measuring from 1 to 5 cm. These subcutaneous deposits were especially noted over the abdominal wall, chest wall, neck, groin, and right thigh. Within the peritoneal cavity two large foci located near the attachment of the abdominal muscles to the lower ribs in the anterior axillary line were noted. Scattered small flakes of calcium were seen deposited between the internal and external oblique muscles. In the walls of the individual alveoli were calcium deposits. There was unusual calcification in the branches of the mesenteric artery. There were extensive calcium deposits in the walls of the subintimal tissue of the small vessels of the lung. The choroid plexus contained calcium deposits. The retroperitoneal lymph glands were markedly enlarged and, as a whole, soft in character, although a few contained calcium deposits. The thyroid gland was of normal size, and careful search showed no evidence of parathyroid tissue. There was tumor invasion of the retroperitoneal lymph nodes, mesenteric lymph nodes, liver, kidneys, periaortic lymph nodes, lungs (questionable), pituitary, dura mater, leptomeninges, cortex of brain, and diffuse skeletal involvement.

Microscopic diagnosis was primary retroperitoneal lymphosarcoma, with diffuse calcinosis.

SUMMARY

The purpose of this monograph is to report a case of calcinosis in which metastatic lymphosarcoma, primary in the retroperitoneal lymph glands, was present. In reviewing the literature, mention is made of very few instances in which malignant tumors should be considered as one of the etiologic factors in production of calcinosis, but no specific examples have been given, so far as the writer can ascertain. Lazarus and Davidsohn [1] have mentioned Wallgreen as having had a patient with a case of multiple myelomas with calcinosis and Wells as observing cases of sarcoma and carcinoma.

Many etiologic factors have been given, such as scleroderma; hyperparathyroidism; renal insufficiency; vitamin D deficiency; destructive bone disease (such as osteomyelitis); Raynaud's disease; leukemia; Paget's disease; multiple myeloma; benign and malignant tumors; mechanical or physical trauma; low protein diet, with a deficiency in choline, and an endocrine disturbance. Hamilton [2] mentions two factors that must be considered: (1) impairment of tissue vitality by some injury or preexisting pathologic condition and (2) infection of some hematogenous organism or toxins.

Brooks [3] mentioned the fact that metastatic calcification may be produced experimentally by toxic doses of vitamin D; whereas Miller [4] reported a case of calcinosis due to the prolonged treatment of a duodenal ulcer with milk and absorbable alkali. According to Costello,[5] unabsorbed dead or degenerated tissue will undergo demineralization.

1. Lazarus, P., and Davidsohn, C.: Hirnhautsarkom mit zahlreichen Kalkmetastasen im Herzen, Ztschr. klin. Med. **60**:314-328, 1906.

2. Hamilton, A. R.: Calcinosis, J. Bone & Joint Surg. **33-B**:572-577, 1951.

3. Brooks, W. D. W.: Calcinosis, Quart. J. Med. **3**:293-319, 1934.

4. Miller, J. M., and others: Calcinosis Due to Treatment of Duodenal Ulcer, J. A. M. A. **148**:198-199, 1952.

5. Costello, M. J.: Cutaneous Calcinosis, New York J. Med. **35**:1266-1271, 1935.

Wheeler [6] mentions bone disease as an etiologic factor due to "abnormality of calcium and/or phosphorous regulation, remote from the site of deposits."

Clinically this case presented such bizarre signs and symptoms that a definite diagnosis was not made until autopsy. Osteitis fibrocystica, multiple myeloma, and Albright's syndrome were considered the most probable. The original results of biopsy and the roentgenograms indicated the possibility of an osteitis fibrocystica with the accompanying high calcium and low phosphorous levels, and yet the alkaline phosphatase readings were not abnormally high until just before death. Multiple myeloma was practically ruled out by the absence of the Bence Jones protein in 22 specimens, one of which was not conclusive (I am cognizant of the fact that the Bence Jones protein may never be detected); there was no inversion of the albumin-globulin ratio, and the age of the patient tentatively precluded this affection.

The pronounced brownish discoloration of the skin of the lower abdomen, hips, back, and upper portion of the thigh, together with the marked hirsutism of the upper and lower legs and with the skeletal involvement, pointed to the possibility of Albright's syndrome.

One can only hypothesize upon the etiologic factor or factors causing the generalized calcinosis in this particular case; it would appear that tissue vitality was impaired by the diffuse bone and soft tissue lesions and that an endocrine disturbance had occurred and was due, perhaps, to the abnormality of calcium and/or phosphorus regulation remote from the site of deposit. And yet one cannot rule out the possibility of an aberrant parathyroid, which was not discovered at autopsy, although a meticulous search was made for it.

6. Wheeler, C. E., and others: Soft Tissue Calcification, with Special Reference to Its Occurrence in the "Collagen Diseases," Ann. Int. Med. **36**:1050-1075, 1952.

SOLITARY AIR CYST OF PERITONEAL CAVITY

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ALTHOUGH multiple air cysts of the peritoneum (pneumatosis intestinales, pneumatosis cystoides intestinalis) have been frequently described in the literature, a careful search has failed to reveal an account of a large solitary air-filled cyst in this location, although Brown,[1] in 1936, reported an air cyst of the abdomen and left thigh, probably formed within the fascia of the psoas muscle. The first case report of multiple gas cysts of the intestine in the human, was described by Bang[2] in 1876. Finney,[3] in 1908, wrote of his first American occurrence, although the condition was known in domestic hogs since 1825. Numerous others were reported until in 1925, Thoma and Hennigar[4] mentioned 57 such cases. In no previous report has a solitary large unilocular cyst resembling that in the case to be described appeared. Potter[5] reports two instances of elongated cysts, one 6 cm. in diameter and 8 cm. in length in the ileum and the other only approximately 1 cm. in diameter in the wall of pylorus. These, however, had outer muscular layers which were fused with that of the viscus and thus were actually intramural rather than intraperitoneal structures.

REPORT OF A CASE

A white nurse, age 45, entered the Conemaugh Valley Memorial Hospital on Nov. 30, 1949, because of the presence of a central abdominal mass, with an associated loss of 10 lb. (4.5 kg.) in weight, weakness, dizziness, occasional abdominal pain, vomiting, and elevation of temperature (102.4 F. maximum). She had the first recent severe attack of vomiting with indefinite abdominal pain on Nov. 12, the mass appearing approximately one week later. She discovered that it moved to the highest part of her abdomen. If she lay on her left side, the mass could be felt in the right periumbilical area; if she lay on the right side, it shifted to the left. The first remembered episode of vomiting occurred in the fall of 1944, when she was serving as a Navy nurse. Several months later this was repeated, with diarrhea and temperature of 101 F. In September, 1946, she again had pain in the left upper quadrant, anorexia, general malaise, and mild fever, which in three or four days subsided. In December, 1947, because of severe headaches and the passing of much intestinal gas, she was given a physical examina-

From the Departments of Surgery and Pathology, Conemaugh Valley Memorial Hospital.

1. Brown, S.: Air Cyst in the Abdomen and Left Thigh, J. Med. **17**:25, 1936.

2. Bang, B. L. F.: I uftholdige kyster i väggen of aleum og i nydannet bindeväv på sammes serosa, Nord. med. **8**:1, 1876.

3. Finney, J. M. T.: Gas Cysts of the Intestine, J. A. M. A. **51**:1291, 1908.

4. Thoma, G. W., and Hennigar, C. R.: Pneumatosis Intestinalis, with Chronic Intestinal Obstruction; Report of Case, Am. J. Clin. Path. **22**:765, 1952.

5. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, Year Book Publishers, Inc., 1952, p. 313.

Fig. 1.—Flat plate demonstrating radiolucent cyst.

Fig. 2.—X-ray of radiolucent cyst.

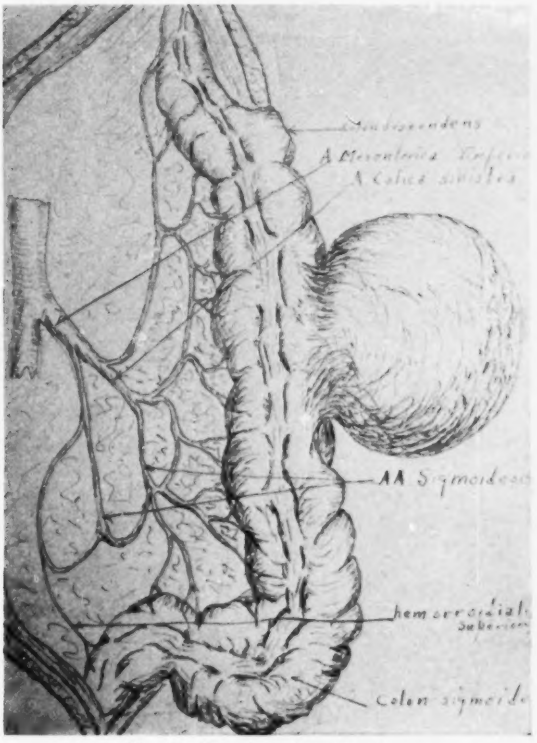

Fig. 3.—Drawing of cyst in situ.

Fig. 4.—Cyst wall.

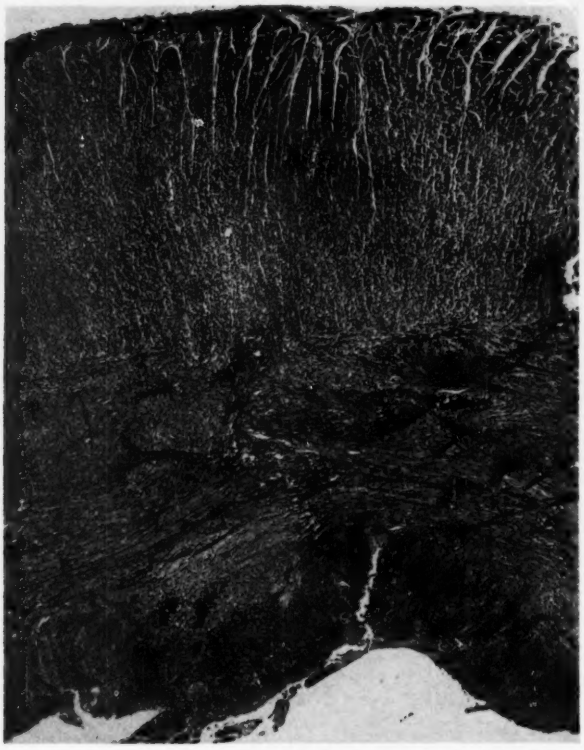

Fig. 5.—Cyst wall.

Fig. 6.—Cyst wall.

tion, with many laboratory tests. Occult blood was present in the stools. She was discharged from the Navy with a diagnosis of uterine fibrosis, cervical erosion, and multiple colonic diverticuli.

On admission, examination revealed a spherical mass in the right upper quadrant which moved easily upon deep inspiration. There was no tenderness, rigidity, or rebound tenderness. Peristalsis was active. Temperature was 98.6 F.; pulse rate was 80 per minute; rate of respiration was 20 per minute; complete blood cell count and urinalysis were normal. X-ray revealed a large rounded symmetrical area of radiolucency in the midabdomen without evidence of in-

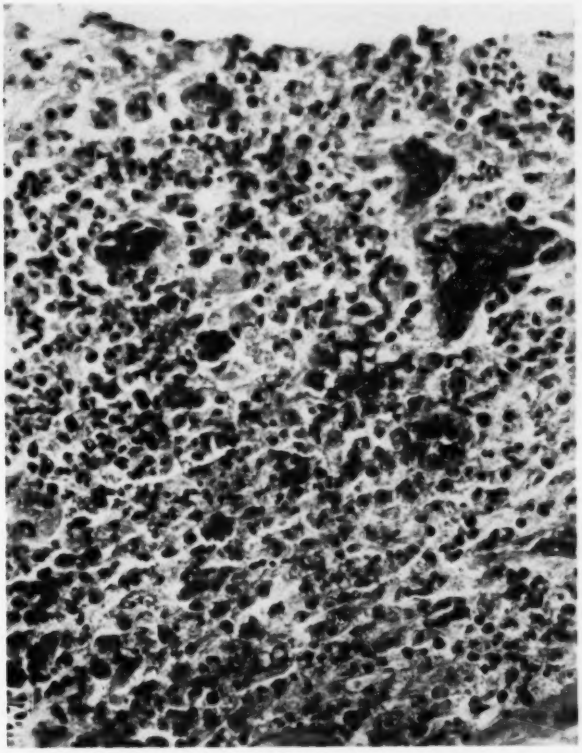

Fig. 7.—Cyst wall demonstrating granulomatous inflammation.

ternal structure. This appeared to be a cyst, but the intense radiolucency indicated the possibility that it contained air or gas. Results of an intravenous pyelogram and barium enema were negative.

On Dec. 3, 1949, laparotomy revealed a cystic mass in the left lower quadrant of the abdomen the size of a large grapefruit which was covered by omentum and which was adherent in a few areas. This however was easily removed, and the mass was found to rise from approximately the midportion of the sigmold colon on the antemesenteric border. It was freely movable and attached by a pedicle of what appeared to be fibrous tissue 5 cm. in length and 2 cm. in diameter. The mass had the feeling "of an inflated balloon." Resection of the mass was attempted, but, on removal, the base of the cyst was broken into, and the escape of odorless gas was noted. A portion of sigmoid 5 cm. long was resected together with the cyst, and end to end anastomosis was performed, with uneventful recovery.

The pathologic report described an already opened cyst approximately 10 cm. in diameter having a smooth grayish pink external surface and a wall varying in thickness from 0.3 to 0.6 cm. The internal lining was smooth and grayish pink in color, and the cross section of the wall was homogeneously grayish-pink. Microscopic examination revealed no evidence of an epithelial lining, the inner surface being composed of a thin layer of necrotic tissue richly infiltrated with lymphocytes, histiocytes, polymorphonuclear leucocytes, and plasma cells with many fibroblasts and new capillary blood vessels. There was an inner circular and an outer longitudinal layer of smooth muscle resembling that seen in the large intestine. The external layer was serosa identical with that of the peritoneal covering of the large bowel. Between the interstices of the muscle bundles, particularly between the inner circular and outer longitudinal layer, were present collections of lymphocytes and plasma cells with a minimal fibrous tissue reaction.

COMMENT AND SUMMARY

In this case it may be speculated that, because of partial obstruction to the neck of an infected diverticulum, air entered the diverticular lumen under pressure and remained entrapped, with consequent gradual stretching and dilatation of its covering, which was derived from the intestinal wall. Subsequently, the orifice became occluded and sealed by a healing process. A more logical explanation however, may reside in the assumption that this cyst was derived from a congenital duplication of the large intestine.[5] This solitary air-filled cyst of the sigmoid peritoneum is believed to be unique in the literature.

1086 Franklin St.

OSTEOMYELITIS PUBIS DUE TO PSEUDOMONAS AERUGINOSA TREATED WITH POLYMYXIN B SULFATE

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OSTEITIS and periostitis of the pubis have been known to occur as complications after surgery of the urinary bladder and prostate. An excellent description and discussion of this complication is given by Dr. Maurice Muschat.[1] The case to be reported here is typical of the condition, except that the offending organism isolated from the involved area is a different one from those reported in the literature. Of the Gram-negative organisms infecting the genitourinary tract Pseudomonas is a common one, especially after instrumentation. This blue-green pigment-producing organism, once believed to be a harmless saprophyte living in water and soil, is now definitely found to be capable of producing deep-seated abscesses in various parts of the body, from which pure cultures have been isolated.

This 60-year-old white man was admitted to Wesley Memorial Hospital for the first time on Dec. 17, 1952, complaining of difficulty of urination and recurrent right lower quadrant pain of several years' duration. A suprapubic prostatectomy was performed on Dec. 18, 1952, and an exploratory laparotomy was done on Jan. 12, 1953, at which time cholecystectomy and division of Lane's kink were performed. Recovery was uneventful, and the patient was discharged from the hospital on Jan. 21, 1953.

He was readmitted to the hospital on Feb. 24, 1953, complaining of severe pain in the groin, perineum, and over the pubic symphysis. This pain started about a month prior to his second admission to the hospital and gradually became worse, necessitating administration of morphine. The pain was aggravated on motion, and the patient could not walk. X-rays of the pelvis revealed a destructive process in the pubic symphysis and the lower public rami. The laboratory findings were normal, except for an accelerated sedimentation rate of 57 mm. in one hour by the Wintrobe method. Physical examination showed a diffuse swelling over the pubic symphysis. The lower extremities were held in semiflexed position and were resistant to passive motion.

The patient was administered oxytetracycline (Oral Suspension Terramycin), 250 mg. every six hours, and on the fourth day after admission the region was explored through a transverse suprapubic incision. The findings were consistent with acute osteomyelitis of the pubic bone with a purulent discharge and sequestrum formation. A specimen of the purulent discharge was collected for culture, and the fibrocartilage of the symphysis and the inferior pubic rami were chiseled and curetted. The patient continued to receive oxytetracycline, 250 mg. every six hours, for three more days, at which time the culture was reported to show a heavy growth of Pseudomonas aeruginosa, and the in vitro sensitivity tests revealed the micro-organism to be sensitive to 5 γ per milliliter of polymyxin B sulfate, 10 γ per milliliter of chloramphenicol; whereas chlortetracycline (aureomycin), dihydrostreptomycin, bacitracin, erythromycin, oxytetracycline, and penicillin were ineffective.

On March 4, administration of intramuscular injections of polymyxin B sulfate,[2] 50 mg. every eight hours, was begun. In addition, the wound was irrigated daily through the drain with 1%

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1. Muschat, M.: J. Urol. **54**:447-458, 1945.

2. The polymyxin B (Aerosporin) sulfate was supplied by Burroughs Wellcome & Company, Inc., through the courtesy of Dr. W. P. Colvin and Dr. D. S. Searle.

solution of polymyxin B sulfate. After five days of polymyxin B sulfate therapy, a second culture of the discharge, taken before the daily irrigation of the wound, showed an occasional Ps. aeruginosa and numerous nonhemolytic streptococci, and the in vitro sensitivity tests showed that bacitracin was the most effective antibiotic. On the basis of this in vitro sensitivity test a solution containing 50 mg. of polymyxin B sulfate and 2,500 units of bacitracin in 5 ml. of sterile distilled water was used for the daily irrigations of the wound, and the administration of intramuscular injections of polymyxin B sulfate was continued as before. After seven days of this combined therapy, another culture revealed only an occasional nonhemolytic streptococcus. The patient improved gradually and was able to be up and around. The same program of therapy was continued for an additional five days. He was discharged seven days after the discontinuance of all therapy. The wound closed shortly after the removal of the drain, and the patient was feeling well and was able to walk with ease.

Daily urinalysis and blood cell counts did not show any untoward reaction to the polymyxin B sulfate therapy. The only complaints during therapy were occasional pain at the site of the injection and occasional circumoral numbness.

SUMMARY AND CONCLUSIONS

A case of osteomyelitis of the pubic bone one month after a suprapubic prostatectomy, its diagnosis and active treatment by incision and drainage, and antibiotics to which the offending organism was found sensitive are reported. This condition should be suspected in every patient complaining of pain in the groin after such intervention. Failure at correct diagnosis or resort to conservative treatment has cost the sufferer up to 18 months of agonizing pain and deterioration of morale, besides the tremendous financial load.

CARCINOMA OF MECKEL'S DIVERTICULUM

Report of Case with Summary Review of the Literature

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DESPITE the rather recent voluminous literature concerning Meckel's diverticulum and despite the great variety of pathological conditions encountered in this structure, carcinoma originating in Meckel's diverticulum remains a surgical and a pathological curiosity. In 1939 Skinner and Walters,[1] in a comprehensive review of the subject, found six authenticated cases of carcinoma arising in a Meckel's diverticulum, and since that date three additional case reports have appeared.

We wish now to add one more case report, which will be the 10th recorded in the literature available to us.

Meckel's diverticulum, said to be present in 2% of all adults, results from incomplete closure of the yolk stalk (omphalomesenteric duct) during the fourth or fifth week of fetal life. The diverticulum is, as a rule, located on the antimesenteric border of the ileum at a distance of 25 to 100 cm. proximal to the ileocecal valve, but, according to Nygaard and Walters,[2] it may be found anywhere in the gastrointestinal tract, from the cardia to the rectum. It occurs three times more frequently in males than in females. The length of the diverticulum, the thickness of its wall, the size of its lumen, as well as the opening between it and the intestine may vary considerably. Usually the end of the diverticulum is free, but it may be adherent to any adjacent structure.

Histologically, it usually contains all the cellular elements making up the wall of the ileum, though the circular musculature may be absent. According to Moore,[3] from 15 to 20% contain islands of jejunal or duodenal mucosa, an additional 15 to 20% contain gastric mucosa, and an occasional one contains pancreatic tissue. Thus, according to Costich and McNamara,[4] in addition to tumors arising from the normal cellular structures of the diverticulum, others arising from these aberrant tissues may be found. Gray and Kernohan [5] have reported a case of carcinoma of Meckel's

From the Departments of Pathology and Surgery, The Vicksburg Clinic.

1. Skinner, I. C., and Walters, W.: Leiomyosarcoma of Meckel's Diverticulum with Roentgenologic Demonstration of the Diverticulum: Report of Case, Proc. Staff. Meet., Mayo Clin. **14**:102-107, 1939.

2. Nygaard, K. K., and Walters, W.: Malignant Tumors of Meckel's Diverticulum: Report of a Case of Leiomyosarcoma, Arch. Surg. **35**:1159-1172, 1937.

3. Moore, R. A.: Textbook of Pathology: Pathologic Anatomy in Its Relation to Causes, Pathogenesis, and Clinical Manifestations of Disease, Philadelphia, W. B. Saunders Company, 1944, p. 837.

4. Costich, K. J., and McNamara, W. L.: Carcinoma of Meckel's Diverticulum: Case Report, Ann. Surg. **124**:503-507, 1946.

5. Gray, H. K., and Kernohan, J. W.: cited by Nygaard and Walters.[2]

diverticulum arising from aberrant gastric mucosa. Nygaard and Walters [2] hypothesize that other carcinomas of Meckel's diverticulum may have begun in heterotopic or aberrant gastric tissue, with additional growth and spread of the tumor making further differentiation of tissue structures impossible.

According to Nygaard and Walters,[2] pathologic changes occur in 25 to 33% of the cases, yet the vast majority are uncomplicated, cause no symptoms, and are found incidentally at operation or at autopsy. Albright and Sprague [6] have pointed out that gradual development of slight abdominal distention and borborygmi without nausea, vomiting, constipation, or diarrhea may indicate a diverticulum. Tumors arising in the diverticulum cause indefinite primary symptoms referable to the tumor itself and more pronounced secondary symptoms arising from superimposed complications. The tumor may or may not be palpable. As a rule, the symptoms and physical signs depend not so much on the size of the tumor as on the secondary complications, such as bleeding, intussusception, obstruction, perforation, and local or generalized peritonitis.

TABLE 1.—*Reported Cases of Carcinoma of Meckel's Diverticulum*

	Year	Age, Yr.	Type, Etc.
Wiseley [7a]	1931	41	Medullary carcinoma *
Copeland [7b]	1931	?	Adenocarcinoma †
Michael and Bell [7c]	1932	76	Adenocarcinoma
Franke [7d]	1933	54	Adenocarcinoma
Brown [7e]	1933	62	Medullary carcinoma
Gray and Kernohan [5]	1937	37	Adenocarcinoma
Weir [7f]	1937	70	Adenocarcinoma * †
Albright and Sprague [6]	1942	48	Adenocarcinoma *
Costich and McNamara [4]	1946	55	Adenocarcinoma * †

* Known deaths.
† Known metastases.

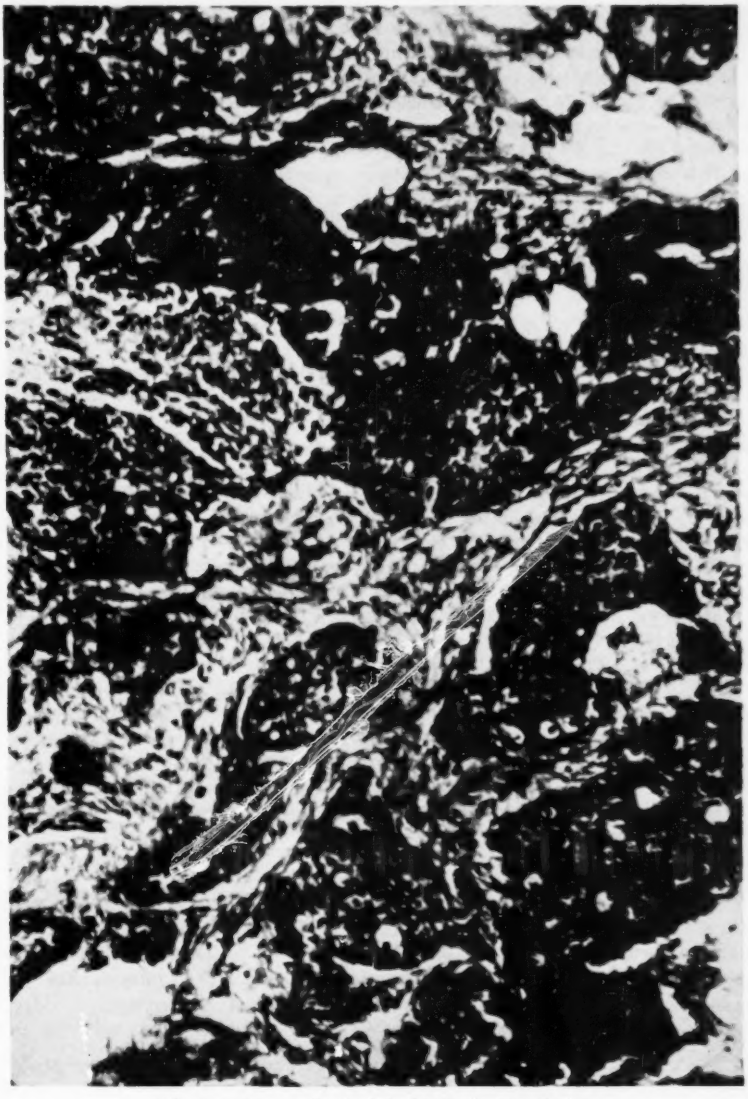
Albright and Sprague [6] emphasize the need for generous resection of both intestine and mesentery well lateral to the diverticulum and its tumor to include any lateral lymphatic extension of the metastases around tumor-blocked vessels in the mesentery.

Of the nine cases previously reported [7] (Table), seven have been identified as adenocarcinoma and two as medullary carcinoma. Six cases occurred in men and two in women while the sex in one case was not stated. The ages of the patients varied from 37 to 76 years. With the exception of the case of Weir,[7f] all of these cases were surgical cases in which removal of the diverticulum, its tumor, and portions of the intestine and mesentery was accomplished. In Wiseley's case [7a] the patient died three days postoperatively, and an autopsy showed no metastasis. In the case of Costich and McNamara,[4] the patient died one week postoperatively, and

6. Albright, H. L., and Sprague, J. S.: Primary Adenocarcinoma in the Meckel's Diverticulum, New England J. Med. **226**:142-146, 1942.

7. (*a*) Wiseley, A. N.: Medullary Carcinoma of Meckel's Diverticulum: J A. M. A. **96**: 1949-1950, 1931. (*b*) Copeland, M. M.: Cited by Wiseley.[7a] (*c*) Michael, P., and Bell, H. G.: Primary Adenocarcinoma Arising in a Meckel's Diverticulum, Surg., Gynec. & Obst. **54**:95-97, 1932. (*d*) Frankie, K.: Cited by Nygaard and Walters.[2] (*e*) Brown, R.: Carcinoma of Meckel's Diverticulum, S. Clin. North America **13**:1283, 1933. (*f*) Weir, J. M.: Carcinoma of Meckel's Diverticulum: Report of a Case, Arch. Path. **24**:791-793, 1937. (*g*) Costich and McNamara.[4] (*h*) Gray and Kernohan.[5] (*i*) Albright and Sprague.[6]

an autopsy showed extensive metastasis to the liver. In Weir's case [7f] carcinoma was discovered at autopsy, and it showed extensive metastases to the liver, omentum, and loops of intestine.



Adenocarcinoma, Grade III; Meckel's diverticulum.

REPORT OF CASE

M. B., a Negro woman, aged 72 years, was admitted to the Lutheran Hospital on July 14, 1947, having been referred by her local physician who had established a tentative diagnosis of appendiceal abscess of several days' duration.

On admission the temperature was 99 F. The blood pressure was 158/100, and there were signs of moderate myocardial failure. The abdomen was slightly distended, and there was an extremely tender oval-shaped mass in the right lower abdominal quadrant. The physical examination was not otherwise remarkable.

The leucocyte count was 18,300, with 87% polymorphonuclear neutrophilic leucocytes; the erythrocyte count was 4,690,000, with 76% hemoglobin. The reaction to the Kahn test was negative. The urine gave a 1 + reaction for albumin and showed occasional pus cells.

The patient was subjected to surgery (W. H. P.), with the use of general anesthesia, on the morning of July 16. After a considerable amount of purulent material was evacuated from the pelvic portion of the peritoneal cavity, the mass was found to be a large Meckel's diverticulum, with a tumor the size of a golf ball comprising the distal end. The proximal and middle thirds of the diverticulum were the seat of an extensive suppurative inflammation, and a perforation existed in the middle third of its wall. There were numerous enlarged nodes in the adjacent mesentery, and a rapid frozen section examination of one node revealed a metastatic carcinoma. The vermiform appendix was normal in appearance.

The terminal ileum containing the diverticulum, the tumor, and considerable mesentery were removed. Continuity was reestablished by side-to-side anastomosis of small to large bowel. No attempt was made to determine the extent of metastases because of the localized suppurative peritonitis.

In spite of extensive antibiotic therapy and the usual postoperative care, the postoperative course was septic in nature, and the patient died five days later of generalized suppurative peritonitis. Permission for autopsy could not be obtained.

Gross Pathology.—The surgical specimen consisted of a 16 cm. length section of terminal ileum with a 9 cm. length diverticulum originating 7 cm. proximal to the ileocecal junction. The diverticulum was thick-walled throughout its length, and its lumen communicated freely with the lumen of the ileum. The free (distal) end of the diverticulum consisted of a solid tumor mass of firm, granular, grayish-white tissue measuring 5 cm. in diameter. There was a suppurative inflammation of the proximal two-thirds of the wall of the diverticulum, with an area of necrosis and perforation in the middle third of its wall. A considerable amount of mesentery was attached to the ileum, and this contained numerous, discrete, firm, grayish-white, oval-shaped nodules measuring up to 2 cm. in length.

Histopathology.—There was no evidence of aberrant tissue in the diverticulum. The tumor was composed of irregular masses of elliptical cells showing feeble attempts at gland formation (Figure) and invasion of the wall of the diverticulum. The individual cells showed marked irregularity in size, staining quality, and mitotic activity. Parts of the tumor, as well as the diverticulum, showed necrosis and infiltration with polymorphonuclear neutrophiles.

Diagnosis.—The diagnoses were primary adenocarcinoma, Grade III, with metastases to mesenteric lymph nodes; acute diffuse suppurative diverticulitis with gangrene and perforation, and Meckel's diverticulum.

SUMMARY

Meckel's diverticulum, an anomalous organ of the gastrointestinal tract, occurring in 2% of adults and more frequently seen in males than in females (3:1), is the site of a variety of recognized pathological conditions. Primary malignant tumors of this organ, however, are relatively rare, with only 17 cases of sarcoma and 9 cases of carcinoma having been reported. A 10th case of primary carcinoma of Meckel's diverticulum is herewith added to the literature.

No definite conclusion regarding the diagnosis, treatment, or prognosis of Meckel's diverticulum can be offered because of the small number of cases reported at present.

SPONTANEOUS RUPTURE OF THE ESOPHAGUS

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SPONTANEOUS rupture of the esophagus is an uncommon occurrence. Considerable data concerning the classic picture of this condition have been collected in the recent literature,[1] yet, as in our case, the diagnosis is missed in about 80% of the reported cases.

Rupture should be distinguished from perforation, although both conditions invoke the same syndrome. Perforation is caused by trauma, such as instrumentation or foreign bodies, and by ulcers or tumors, which ulcerate or erode the esophageal wall. Spontaneous rupture occurs in an apparently normal esophagus after prolonged forceful vomiting, drinking bouts, straining at stool, lifting of a heavy weight, convulsive seizure, parturition, or without any known cause.

The mechanism of this condition is not exactly known. Mackler [1a] believes that it is caused by increased intraesophageal pressure transmitted from the stomach. In 65 fresh human cadavers he inflated and ruptured the esophagus. The rupture always occurred in the left lateral wall at the lower end of the esophagus, apparently the weakest part of the organ. The site and configuration of these experimental ruptures were similar to those observed in three clinically studied cases. These investigations have been confirmed.[2]

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1. (*a*) Mackler, S. A.: Spontaneous Rupture of Esophagus: Experimental and Clinical Study, Surg. Gynec. & Obst. **95**:345, 1952. (*b*) Ware, G. W.; Shnider, R. I., and Davis, E. W.: Spontaneous Rupture of Esophagus: Report of a Successful Case with Cardiac Arrest and Review of the Literature, A. M. A. Arch. Surg. **65**:723, 1952. (*c*) Gay, B. D., Jr.: Esophageal Perforations: A Review of Etiology with Representative Case Presentations, Am. J. Roentgenol. **68**:183, 1952. (*d*) Kinsella, T. J.; Morse, R. W., and Hertzog, A. J.: Spontaneous Rupture of Esophagus, J. Thoracic Surg. **17**:613, 1948. (*e*) Flipse, M. E.: Spontaneous Rupture of Esophagus, Dis. Chest **19**:165, 1951. (*f*) Philip, W. E., and Comer, J.: Spontaneous Rupture of Esophagus: Report of 2 Cases, Ann. Int. Med. **34**:1258, 1951.

2. Burt, C. A.: Pneumatic Rupture of Intestinal Canal: With Experimental Data Showing the Mechanism of Perforation and Pressure Required, Arch. Surg. **22**:875, 1931. Hertzog, A. J., and Leighton, R.: Spontaneous Perforation of Esophagus: Minnesota Med. **29**:442, 1946. Ware, Shnider, and Davis.[1b]

Ware and his associates [1b] suggested that this clinical entity was usually associated with vomiting and that repeated stimuli caused fatigue of the vomiting center and probably "confusion" in the coordination of the act of vomiting. This theory may particularly apply to cases of acute alcoholism.

Untreated rupture of the esophagus is usually a fatal disease. Prompt diagnosis and surgical intervention have reduced the mortality rate (in about 20% of cases reported). Suggestive symptoms are vomiting, epigastric and lower thoracic pains, and subcutaneous emphysema.

X-ray examination of the chest is the most valuable test, and the roentgenologist should be familar with the picture.[3] Left-sided effusion is common. Gas may be present in the mediastinum; the diaphragm may be rigid. X-ray visualization of a suspected perforation is possible with the aid of a few drops of iodized oil. The use of barium is contraindicated. Many cases are not typical, and the diagnosis may be mistaken for a ruptured peptic ulcer, cholecystitis, pancreatitis, intestinal obstruction, perforated viscus, spontaneous pneumothorax, pulmonary infarction, myocardial infarction, pleural effusion, pneumonia, or dissecting aneurysm.

The only therapy is surgical. The following measures may be indicated: (1) mediastinum drainage; (2) pleural drainage; (3) suture of the esophagus, and (4) excision of the diseased portion, if necessary and feasible.

In the absence of classic symptoms the diagnosis is easily missed. The case of spontaneous rupture described in this paper developed after herniotomy in a psychotic patient. The only signs and symptoms were vomiting, fever, prostration, pain in the back, and bilateral pneumonia.

REPORT OF A CASE

A Negro man, aged 56, was admitted to this hospital in 1945, with a diagnosis of syphilis, meningoencephalitic type, tertiary, manifested by psychotic reaction. During his stay in this hospital he made a good adjustment and qualified for several home leaves. He returned from one of these leaves in January, 1951, for inguinal herniorrhaphy. His past history revealed that he acquired syphilis in 1940, received extensive treatment, and began to shown signs of psychosis in 1944.

Preoperative physical examination revealed a well-developed Negro man, with a temperature of 99 F., pulse rate 88, respiration rate 18, and blood pressure 118/68. He was cooperative, benign, quiet, and without complaint. He presented a right, indirect, inguinal hernia, which extended into the scrotum. It was reducible. Findings on urinalysis were negative. The white blood cell count was 5,000 and the hemoglobin content 15.3 gm. per 100 cc. The complement fixation for syphilis was 4+; spinal fluid complement fixation, 4+, and colloidal gold, 5555310000.

On Jan. 24, 1951, a classic operation for hernia was performed with the use of local anesthesia, with 1% procaine hydrochloride. The patient withstood the operation well and was out of bed on the same day. During the night after the operation, he complained of pain in the back, which subsided quickly. The next day he was out of bed (Jan. 25). In the afternoon he complained of severe pain in the chest and sacral area and of vomiting. He started coughing and expectorated some clear mucus. On Jan. 26, his temperature was 102 F., pulse rate 126, and respiration rate 40 beats a minute and laborious. He complained of pain in the left chest and of nausea. Examination of the chest revealed dullness in the right base, with rales and increased fremitus. It was felt that he had a right lower lobe pneumonia. "Coffee ground" sputum was

3. Priviteri, C. A., and Gay, B. B., Jr.: Spontaneous Rupture of Esophagus with Report of 5 Cases, Radiology **57**:48, 1951. Gay.[1c]

observed by the nurse. The blood count showed 4,010,000 red blood cells, 13.5 gm. of hemoglobin per 100 cc. and 5,150 white blood cells, with 56% polymorphonuclear leucocytes. X-ray examination of the chest revealed consolidation in the right lower lobe and infiltration in the left base. The patient showed moderate abdominal distention, and gastric lavage produced coffee-ground material. The patient was treated with penicillin and oxygen. On the next day, Jan. 27, his condition was worse. Penicillin, chlortetracycline (aureomycin), and oxygen were continued. On Jan. 28, considerable amounts of liquid were recovered from the stomach with the

Longitudinal rent in posterior esophageal wall, measuring 1.5 cm.

Wangensteen apparatus. The lungs showed signs of bilateral consolidation. The blood pressure was 130/88. Intake and output of fluids were adequate. Abdominal distention receded. At 6:30 p. m., the temperature was 102 F., pulse rate 120, and respiration rate 40. The patient was given 20 mEq. of potassium chloride. Review of the x-rays of the chest showed pneumonitis, or atelectasis on the left side and pleurisy on the right side, with some effusion. The patient died suddenly at 8:45 p. m. on Jan. 28, 1951.

The autopsy disclosed extensive bilateral serofibrinous pleurisy, with partial atelectasis of the left lung. There was no evidence of pneumonia in either lung. Fibrinous pericarditis was present. The posterior mediastinum between the level of the bifurcation of the trachea and the diaphragm

was transformed into a cavity lined by thick, stringy, blackish-gray, fibrinous exudate. At a point 3 cm. below the bifurcation of the trachea the esophageal wall was markedly thickened and edematous, measuring 0.2 to 0.3 cm. in thickness, and in one area contained a small amount of purulent material between its layers. Just at the junction with the cardia, above the diaphragm, there was a longitudinal rent in the posterior esophageal wall, about 1.5 cm. in length, with thin and somewhat ragged edges (Figure). There was minimal inflammatory reaction on gross, as well as on microscopic, examination.

SUMMARY

A case of spontaneous rupture of the esophagus following herniotomy in a patient with meningovascular syphilis is reported. This syndrome should be considered as a postoperative chest complication even in the absence of the classic symptoms.

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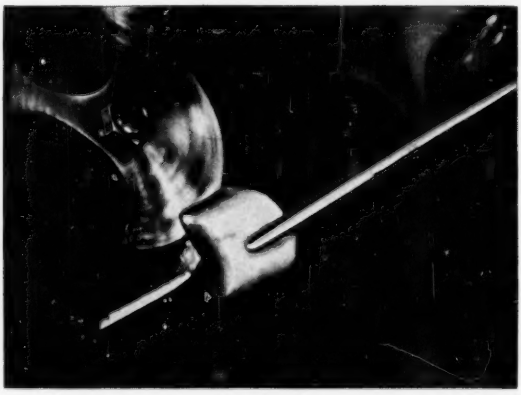

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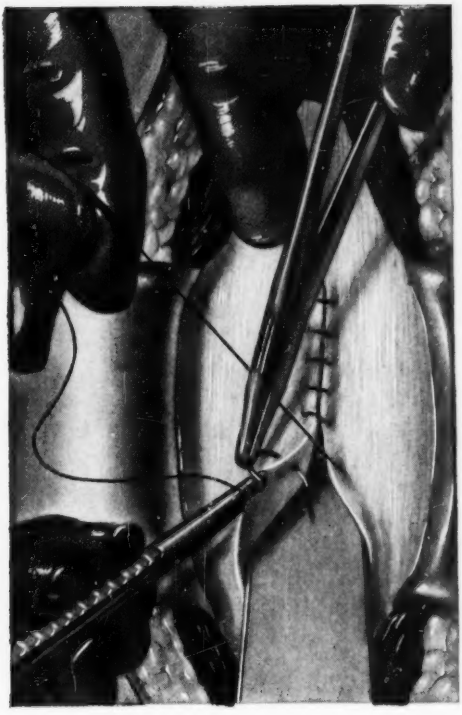

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